COMPARATIVE ANALYSIS OF VISUAL INSPECTION WIH ACETIC ACID, VISUAL INSPECTION WITH LUGOL'S IODINE, CONVENTIONAL PAP SMEAR AND LIQUIPREP™ WITH HISTOPATHOLOGY AS GOLD STANDARD

Dissertation submitted in partial fulfillment of
the requirements for the degree of

M.D. (PATHOLOGY)

BRANCH – III

INSTITUTE OF PATHOLOGY AND ELECTRON MICROSCOPY,

MADRAS MEDICAL COLLEGE,

CHENNAI – 600 003.

THE TAMIL NADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2013

CERTIFICATE

This is to certify that this Dissertation entitled "**COMPARATIVE ANALYSIS OF VISUAL INSPECTION WIH ACETIC ACID, VISUAL INSPECTION WITH LUGOL'S IODINE, CONVENTIONAL PAP SMEAR AND LIQUIPREP™ WITH HISTOPATHOLOGY AS GOLD STANDARD**" is the bonafide original work of **Dr. S.ANITHA RANI**, in partial fulfillment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2013.

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DECLARATION

I Dr. S.Anitha Rani, solemnly declare that the dissertation titled "**COMPARATIVE ANALYSIS OF VISUAL INSPECTION WIH ACETIC ACID, VISUAL INSPECTION WITH LUGOL'S IODINE, CONVENTIONAL PAP SMEAR AND LIQUIPREP^{TM} WITH HISTOPATHOLOGY AS GOLD STANDARD**" is the bonafide work done by me at Institute of Pathology, Madras Medical College under the expert guidance and supervision of Prof. Dr. K. Rama M.D., Professor of Pathology, Institute of Social Obstetrics and Government Kasturba Gandhi Hospital, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of M.D., Degree (Branch III) in Pathology.

Place : Chennai – 600 003.

Date : **Dr. S.ANITHA RANI**

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

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CERTIFICATE OF APPROVAL

To

Dr. S. Anitha Rani
PG in MD Pathology
Madras Medical College /GGH , Chennai -3

Dear Dr. S. Anitha Rani

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled " Comparative analysis of VIA, VILI, LiquiprepTM and conventional pap smear with histopathology as gold standard" No. 02022011.

The following members of Ethics Committee were present in the meeting held on 17.02.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	– Chairperson
2.	Prof. A. Sundaram, MD Dean i/c , Madras Medical College, Chennai -3	– Member Secretary
3.	Prof R. Sathianathan Director , Institute of Psychiatry, MMC,Ch-3	– Member
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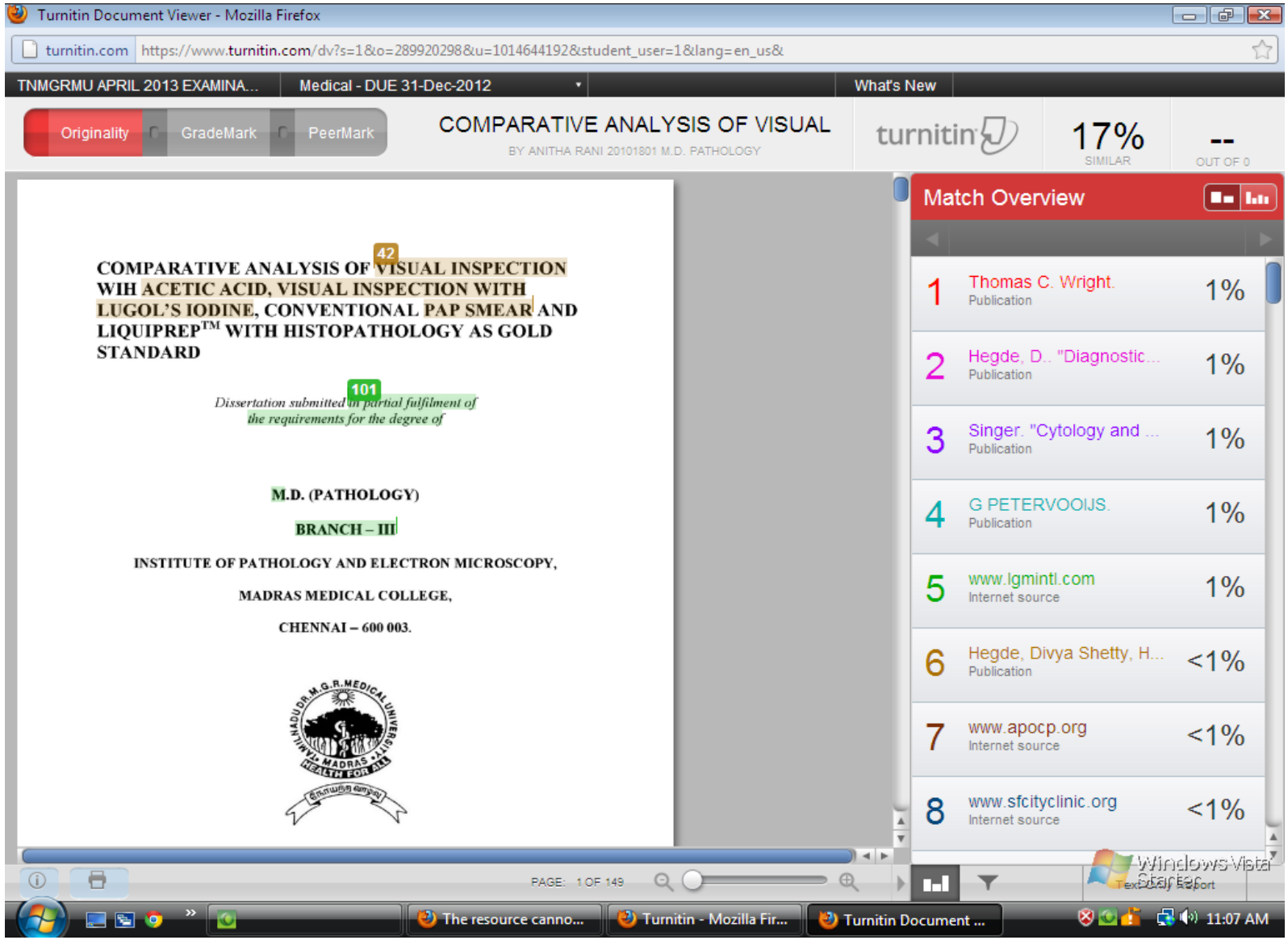
8.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	– Layperson
9.	Thiru. S. Govindasamy . BA.BL	– Lawyer
10.	Tmt. Arnold Soulina	– Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee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COMPARATIVE ANALYSIS OF VISUAL INSPECTION WIH ACETIC ACID, VISUAL INSPECTION WITH LUGOL'S IODINE, CONVENTIONAL PAP SMEAR AND LIQUIPREP TM WITH HISTOPATHOLOGY AS GOLD STANDARD Dissertation submitted in partial fulfilment of the requirements for the degree of M.D. (PATHOLOGY) BRANCH – III INSTITUTE OF PATHOLOGY AND ELECTRON MICROSCOPY, MADRAS MEDICAL COLLEGE, CHENNAI – 600 003. THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY CHENNAI APRIL 2013 CERTIFICATE This is to certify that this Dissertation entitled "COMPARATIVE ANALYSIS OF VISUAL INSPECTION WIH ACETIC ACID, VISUAL INSPECTION WITH LUGOL'S IODINE, CONVENTIONAL PAP SMEAR AND LIQUIPREP TM WITH HISTOPATHOLOGY AS GOLD STANDARD" is the bonafide...

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ABBREVIATIONS

VI	: Visual Inspection
VIA	: Visual Inspection with Acetic acid
VILI	: Visual Inspection with Lugol's Iodine
IARC	: International Agency for Research on Cancer
CIN	: Cervical Intraepithelial Neoplasia
HPV	: Human Papilloma Virus
DNA	: Deoxyribo Nucleic acid
RNA	: Ribo Nucleic Acid
NILM	: Negative for Intraepithelial Lesion or Malignancy
ASCUS	: Atypical Squamous Cells of Undetermined Significance
ASC-H	: Atypical Squamous Cells, cannot exclude HSIL
SIL	: Squamous Intraepithelial Lesion
LSIL	: Low grade Squamous Intraepithelial Lesion
HSIL	: High grade Squamous Intraepithelial Lesion
SCC	: Squamous cell carcinoma
AIS	: Adenocarcinoma- In-Situ
Rb	: Retinoblastoma
ALTS	: Atypical squamous cells/Low grade squamous intraepithelial Lesion Triage Study
NCI	: National cancer institute
TBS	: The Bethesda System
ACOG	: American College of Obstetricians and gynaecologists
HIV	: Human Immunodeficiency Virus

DES : DiEthyl Stilbesterol

LBC : Liquid Based Cytology

LP : LiquiPrep TM

FDA : Food and Drug Association

PCR : Polymerase Chain Reaction

HC : Hybrid Capture

ELISA : Enzyme Linked Immunosorbent Assay

LLETZ : Long Loop Excision of Transformation Zone

LASER : Light Amplification by Stimulated Emission of Radiation

CONTENTS

INTRODUCTION

INTRODUCTION

Carcinoma cervix is one of the leading causes of death among women in developing countries. For each case of cancer of body of the uterus, there are 25 cases of cancer cervix in India. About 5,00,000 new cases of carcinoma cervix are being diagnosed each year out of which 79% occur in the developing countries[1]. The 5 years survival rate is 90% for cervical cancer in the early stage whereas it is much lower (14%) for persons with advanced stage IV disease. The incidence of invasive cervical cancer has come down to a great extent over a span of 40 years, mainly because of early cancer detection programs. A close quarters observation on the social behaviour of our society reveals that most of the women in our country have their marriages at very early part of their life leading to early commencement of sexual activity and poor sexual hygiene which are considered to be important etiological factors for cervical carcinoma[2].

INCIDENCE

In India, the age standardised incidence rate of carcinoma cervix is 30.7 per 100,000 women and the global age standardised incidence rate is 16 per 100,000[1]. The death rate of cervical cancer in India is 6.5 per 1,00,000.

PREVALENCE

A conservative estimate of global prevalence states that there are about 1.7 million cases of clinically recognized cervical cancer and 5-13

million women have precancerous lesions. This estimate is high owing to the addition of new cases each year and also due to the fact that the diagnosed cases do not receive adequate treatment. Current resources about the natural history of cancer cervix suggest that there are two to five times women with potential precursors to cervical cancer such as those with invasive cervical carcinoma. This results in a rough estimate of 7,000,000 women around the world with high-grade dysplasia requiring detection and treatment.

CAUSES OF SCREENING FAILURE IN DEVELOPING COUNTRIES:

- A number of women with cervical cancer do not turn up for investigations and hence are excluded from the cancer registry data resulting in considerably lower estimates of statistical parameters like cancer incidence, prevalence, and disease related mortality.
- Diagnostic facilities do not reach older women or those with financial constraint which pose a great challenge in estimating the current statistics.
- Recording the number of women with cervical cancer is problematic[2] because of the lack of organized health information systems in developing countries like India.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

- To compare the efficacy of VIA, VILI, conventional Pap smear and LiquiPrepTM as screening procedure for carcinoma cervix in patients attending the Gynecology department of Institute of social obstetrics and Govt. Kasturba Gandhi hospital,Chennai.

- To study abnormal smears and do cervical biopsy for those patients.

- To correlate the cytological findings with histopathological diagnosis.

- To evaluate the advantages and disadvantages of conventional Pap and LiquiPrep^{TM} in the screening of cervical lesions.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Cervical cancer is ranked the first among cancers arising in women of the Indian subcontinent, accounting for about 26.1- 43.8% of all carcinomas in Indian women[2]. By virtue of its accessibility, cancer of cervix can be readily diagnosed in its precancerous stage. If treated in the earlier stages the patient can often be cured of the disease. There are various methods of screening for carcinoma cervix.

Gathering data from national programs organized in eight countries, the International Agency for Research on Cancer (IARC) reported a 90% reduction in the incidence of cervical carcinoma if the entire female population is screened at regular intervals[3].

RISK FACTORS ASSOCIATED WITH SIL:

- Number of sexual partners
- Age at first intercourse (especially less than 16 years of age)
- Sexually transmitted diseases- Human papillomavirus, Herpes simplex virus, Chlamydia trachomatis
- Early age of first pregnancy
- Parity

- Low socioeconomic class
- Cigarette smoking
- Human immunodeficiency virus
- Immunosuppression from any cause
- Deficiencies of vitamins
- Interval between the pap smears
- Use of oral contraceptives

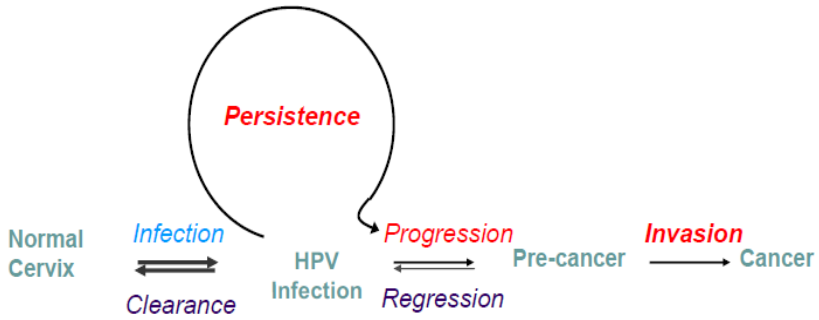
In a study by Parazzini F et al[4] the number of sexual partners and commencement of early sexual activity were independent risk factors for development of carcinoma cervix.

Walboomers JM et al[5] proved the viral aetiology of cancer cervix beyond doubt.

Schiffman et al[6] showed that among those women infected with high-risk types of HPV, the risk can be doubled if associated with other factors such as smoking, immunosuppression, and long-term use of oral contraceptives.

NATURAL HISTORY OF DISEASE:

Understanding the natural history of various stages of CIN is the cornerstone for the appropriate clinical management. In addition to the degree of dysplasia, it is likely that the course of a specific lesion is also influenced by other factors such as the patient's age, inciting HPV type, immune competence and smoking [6].



HUMAN PAPILLOMAVIRUS AND THE PATHOGENESIS OF PRECURSOR LESIONS AND CERVICAL CARCINOMA

- Papanicolaou (1954) was the first person to report on the "perinuclear cavitation" while Koss and Durfee (1956)[7] have commented on the HPV induced change as "koilocytotic vacuolated change"
- Purola and Savia[8] (1977) published their paper on distinctive morphologic lesions in the uterine cervix with characteristic cytopathic effects of HPV similar to the changes seen in genital warts *(condylomata accuminata)*.

- More than 99% of all cervical cancers are considered to be related to HPV independent of racial origin[9].
- HPV is a double-stranded DNA virus and a member of the Papovaviridae family. The various subtypes of HPV are divided into “low-risk” and “high-risk” depending on the risk of carcinoma associated with the infection. Low-risk subtypes are 6, 11, 42, 43, 44, and 53, whereas high-risk subtypes include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56,58, 59, and 68[6].
- The human papilloma virus enters the basal cells or immature squamous metaplastic cells via the mucosal defects in the transformation zone.
- The virus may cause either a nonproductive (latent) or a productive infection.
- In productive infection, large amounts of free DNA virus (episomal) are produced in the intermediate and superficial cell layers. The infected cells mature and migrate towards the surface making obvious the characteristic cytopathic effect – the koilocytic atypia.
- Integration of HPV DNA into the host cell genome, with covalent binding of viral genome into host DNA, is a critical event in the progression to high-grade squamous intraepithelial lesions (HSIL).
- High-risk HPVs produce two proteins E6 and E7, with growth-stimulating and transforming properties. Viral integration into the

host cell genome results in disruption of the viral DNA with overexpression of E6/E7 genes.

- In a study by Werness BA et al[10], increased levels of the E6/E7 viral oncoproteins result in abrogation of p53/Rb tumour suppressor proteins, resulting in uncontrolled cell cycling and proliferative activity of the squamous epithelium.
- It is stated that low-risk HPV is commonly associated with low-grade squamous intraepithelial lesions (LSIL) which frequently regresses, whereas high-risk HPV subtypes can result in either LSIL or HSIL. Moreover, if untreated, HSIL can subsequently progress to invasive carcinoma[11].
- However, a recent multicenter study ("Atypical squamous cells/Low grade squamous intraepithelial lesion Triage Study (ALTS)") has shown that in contrast to previous findings, 83% of women with a LSIL on Pap test had a high-risk HPV subtype.
- Hence, abnormalities associated with HPV may be classified into transient infections regressing over the course of 1 to 2 years and persistent infections which are associated with an increasing risk of development of a precursor lesions of cervical cancer or invasive cancer.[12,13]

APPROXIMATE VALUE OF SPONTANEOUS REGRESSION OR PERSISTENCE AND PROGRESSION OF CIN[14]:

COURSE OF CIN	CIN 1	CIN 2	CIN 3
REGRESSION TO NORMAL	60%	40-50%	33%
PERSISTENCE	30%	40%	55%
PROGRESSION TO CANCER	1%	5%	>12%

SCREENING METHODS FOR CERVICAL CANCER

- Visual screening approaches- Colposcopy
- Conventional Pap Smear
- Liquid Based Cytology
- Automated screening
- HPV Genotyping

VISUAL SCREENING APPROACHES:

Visual screening is a process by which cervical lesions are identified without relying on cytology. Early studies included visual inspection (VI), which involved simply visualising the cervix with the unaided eye to detect any signs of early cancer. Also referred to as

"downstaging," this strategy was not much precise in detecting the cancer precursors.

Pathophysiological basis of VIA:

When acetic acid is applied, normal squamous epithelium presents a pink hue while the columnar epithelium is bright red owing to the reflection of light by the highly vascular stroma. Whitening effect of acetic acid is proportional to the amount of cellular proteins. Areas with the highest nuclear activity and DNA content demonstrate the most dramatic change in colour. Inflammation and healing result in acetowhite areas that are distributed widely and are restricted to transformation zone and quickly disappears. Acetowhitening of CIN takes up promptly and reverses slowly.

Pathophysiological basis of VILI:

On applying iodine, normal squamous epithelium turns mahogany brown since it is glycogen rich. Columnar epithelium is unstained since it does not take up iodine. Areas of CIN and invasive cancer do not stain with iodine and remain saffron coloured or mustard yellow.

Brief history of colposcopy[16]

Colposcopy was introduced by Hans Heinselmann in 1925 at Germany. He stated that it might be possible to detect cervical cancer at

an early stage by adequate illumination and magnification of the cervix. In 1928, Schiller introduced the concept of applying iodine on the cervix to identify unstained glycogen depleted areas for biopsy.

Indications for colposcopy:

- Suspicious looking cervix
- CIN1, CIN 2, CIN 3 or invasive carcinoma on cytology
- Persisting low grade abnormalities
- Persistently unsatisfactory quality on cytology
- HPV infection
- Acetowhite areas on VIA
- Positive lesion on VILI

Advantages of colposcopy:

- Promising tool in low resource settings
- Simple approach
- Not much dependent on infrastructure for adequate performance
- Maintenance is easier and cheaper

- ❖ Both diagnostic and therapeutic procedures can be done.
    - Location of the lesions
    - Selection of biopsy site
    - Determination of treatment of early invasive cancer and CIN
    - Reduction in unnecessary biopsy
    - Management of abnormal smear in pregnancy

Disadvantages of colposcopy:

- ➢ Low specificity when used in asymptomatic women[17].
- ➢ Cost and maintenance of the equipment.
- ➢ Time and skill necessary to do the procedure and interpret the findings.

REPORTING VISUAL INSPECTION FINDINGS[18]

NORMAL

- ❖ Smooth, Pink.
- ❖ External Os: Central Hole, Round – Nullipara, Slit –Multipara.
- ❖ Atrophic – Post Menopausal.

ABNORMAL

- ❖ Infection : Hypertrophy.
- ❖ Ectopy : Redness / Congestion
- ❖ Distortion, simple erosions (Does not bleed on touch)
- ❖ Cervical polyps (With smooth surface)
- ❖ Abnormal discharge (foul smelling, dirty white greenish)
- ❖ Nabothian follicles
- ❖ Suspicious of Maligancy: Lesions that bleeds on touch /irregular surface, friable growth

VIA Positive Acetowhite areas present.

VIA Negative No acetowhite areas.

Various categories are used to classify visual inspection findings.

Category Results

- Ulcerative or exophytic cervical growth suspicious of carcinoma
- Definite Lesion: Acetowhite lesion with well defined border

Non confluent scattered lesion

- Focal: small, punctuated areas of acetowhitening
- Ill defined lesion: Vaguely defined and faintly acetowhite
- No Lesion: No acetowhite lesion

Negative VILI

- Normal Cervix
- Polyps: Areas which appear pale due to no/partial iodine uptake
- Leopard skin appearance is seen in Trichomonas Vaginalis infection
- Satellite lesions: Areas which do not show iodine uptake are seen away from the squamocolumnar junction.

Positive VILI

The result is recorded as positive when dense, bright mustard yellow or saffron –yellow coloured iodine negative areas are visible in the tranformation zone around the squamocolumnar junction or when the entire cervix turns dense yellow.

VILI Positive (Invasive Cancer)

When an irregular, ulcerative or proliferative growth is present on the cervix which changes to yellow colour on application of iodine.

HISTORY AND RECENT ADVANCES IN PAP SMEAR:

- In 1851**,** Robert Hull, introduced the use of vaginal speculum which helped to reveal an epidemic of uterine disease.
- While studying the response of the human vaginal mucosa to hormones, George Papanicolaou discovered that tumor cells can be detected in the vaginal fluid of patients of cervical carcinoma[19]. Papanicolaou published this paper entitled "New Cancer Diagnosis" in 1928[20].
- Aurel Babès, a Romanian pathologist, presented his paper entitled "The possibility of diagnosing uterine cancer by the smear technic" in 1927[21]. Babès elaborated on this paper in April 1928 and clearly stated that his method was applicable to early cancers which had not penetrated the stroma. Later, Kermauner and Schiller had used a modified vaginal smear method for the diagnosis of carcinoma cervix on a large scale with good results[22].
- It was actually a Canadian physician by name J. Ernest Ayre who first studied the procedure which is called pap smear at present in the mid-1940s[23].
- In 1943 J.Ernest Ayre et al, emphasized on the use of cervical os aspiration as a preferable technique for the diagnosis of uterine cancer and published ‘A simple office test for uterine cancer diagnoses’.

- In 1947, Ayre et al used surface biopsy cell scrapping technique with Ayre's spatula[24].
- A conventional pap smear or liquid-based cytology test is the test which is routinely employed for detecting precursor lesions of cervical carcinoma in the cervical cells.

CELL COMPONENTS IN A PAP SMEAR

Basal cells - rarely seen except in atrophic vagina. Small round cells with smooth border and a central round nucleus.

Parabasal cells - uniform round cells with a thick blue or green cytoplasm and large central round nucleus.

Intermediate cells - polyhedral cells with thin semitransparent pink to blue cytoplasm and central large vesicular nucleus. A folding or curling tendency of the edges (navicular cells) is seen in pregnancy.

Superficial cells - most common and largest epithelial cell in a pap smear. Polyhedral cells with a thin homogenous cytoplasm pink to orange (if keratin is present). Nucleus is central and pyknotic.

Endocervical cells - ciliated or nonciliated cells, honeycomb or picket-fence pattern depending on the view.

Endometrial cells - can also be seen depending on the site of collection.

PAP SMEAR NOMENCLATURE[25]:

Papanicolaou Class system (1954)	**Descriptive (1968)**	**CIN (1978)**	**Bethesda system (1988)**
Class I	Negative for malignant cells	Negative	Within normal limits
Class II	Inflammatory atypia Squamous atypia Koilocytic atypia	Negative	Reactive and reparative changes Atypical squamous cells of undetermined significance
Class III	Mild dysplasia Moderate dysplasia Severe dysplasia	CIN I CIN II CIN III	LSIL HSIL HSIL
Class IV	Carcinoma in situ	CIN III	HSIL
Class V	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

THE BETHESDA SYSTEM[26]

As seen above, the terminology used in cervical cytology has evolved over the course of many years. In1988, National cancer institute (NCI) working groups coined uniform descriptive terminology for cervical cytology and named it as 'The Bethesda System (TBS)'.The 1988 Bethesda system of reporting cervix/vaginal cytology divided squamous intra epithelial lesions into the following categories.

1. Atypical squamous cells of undetermined significance (ASCUS)

2. Low Grade SIL

3. High Grade SIL

4. Squamous cell carcinoma

The main criticism of this system was that many individuals whose smears were designated Low Grade SIL category were overtreated. Hence minor changes were made in the 1991 Bethesda system which modified the terminology. The committee also laid down criteria for adequacy of the specimen and diagnostic terms in a TBS atlas which outlines and illustrates the important cytologic features. The Bethesda System (2001) is currently in use.

The Bethesda System includes three factors namely,

a. Statement of specimen adequacy

b. General categorization

c. Diagnostic terminology

A. SPECIMEN ADEQUACY

An adequate specimen is described in positive terms as a correctly labelled one, provided with the necessary clinical information, adequately fixed and on microscopic examination demonstrates an appropriate number of well preserved and evenly distributed cells which includes an ectocervical and an endocervical component. For conventional pap, minimum of 8,000-12,000 and for liquid based cytology a minimum of 5,000 squamous epithelial cells which are adequately preserved and well visualized are considered to be “satisfactory for evaluation”. An adequate endocervical / transformation zone component consists of ten well preserved cells occurring individually or in groups. Mitchell and Medley[27] proved that the presence of endocervical cells is not a criterion when the detection rate of endocervical cells is high, especially when a cytobrush is used.

B. GENERAL CATEGORIZATION

1. NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY

Smears with no epithelial abnormality are recorded as “Negative for intraepithelial lesion or malignancy” (NILM).

- **Infections**:
  - Trichomonas vaginalis
  - Fungal organisms morphologically consistent with Candida species.
  - Shift in flora suggestive of bacterial vaginosis
  - Bacteria morphologically consistent with Actinomyces species.
  - Cellular changes consistent with herpes simplex virus
- **Reactive cellular changes**:

Reparative change can manifest as regeneration of cells which involves the squamous epithelium, squamous metaplastic epithelium and columnar epithelium.

Reparative reactions are frequent in women with recurrent cervicitis and recent treatment such as conization, punch biopsies, laser therapy, cryosurgery and endocervical curettage.

Colgan et al[28] suggested that cells from reparative epithelium lack reproducibility and appear as sheet like aggregates with ill defined cytoplasmic borders.

The cytoplasm is finely vacuolated and cyanophilic.

Nuclei appear round to oval with variable degree of nuclear enlargement and altered size of nuclei. The cells have prominent nucleoli with evenly distributed and finely granular chromatin but the nuclei are not hyperchromatic.

2. EPITHELIAL ABNORMALITES

ASCUS (ATYPICAL SQUAMOUS CELLS OF UNDERTERMINED SIGNIFICANCE)

- ASC refers to smears in which the cytologic changes suggest SIL, but are insufficient either qualitatively or quantitatively to give a definitive interpretation[29].

- Criteria

    - Nuclei are about two and a half to three times the size of the nucleus of a normal intermediate type of squamous cell [30].

    - Mild increase in nuclear cytoplasmic ratio.

    - There is minimal nuclear hyperchromasia and mildly irregular chromatin distribution.

ATYPICAL SQUAMOUS CELLS, CANNOT EXCLUDE HSIL (ASC-H)

- Criteria

    - Cells occur singly or in small fragments of less than 10 cells.

    - Cells approximate the size of metaplastic cells with nucleus of size 1½ to 2½ times larger than normal. Nuclear cytoplasmic ratio may be similar to that of HSIL.

    - Nuclear variations like chromatin irregularity, hyperchromasia, and altered nuclear shapes showing focal irregularity are in favour of HSIL.

    - The rate of ASCUS is generally less than 5% in low risk population. The rate of ASCUS although higher in high risk population, it should not be more than two to three times the percentage of SIL.

- Sherman ME et al[31] concluded that in 25% to 60 % of patients with ASCUS, further evaluation will detect a squamous intraepithelial lesion.

SQUAMOUS INTRA EPITHELIAL LESIONS (SIL)

In the Bethesda system, low grade squamous intraepithelial lesion (LSIL) and high grade squamous intra epithelial lesion (HSIL) constitute the spectrum of precursor lesions of cancer cervix.

LSIL:

CYTOLOGY

- Changes in the squamous cell associated with HPV infection include “mild dysplasia” and “CIN 1.”

- Both lesions exhibit similarity in biologic behaviour, inciting HPV types and clinical management, thereby coming under a common terminology of LSIL[32,33].

- Criteria

  - Reagan et al[34] demonstrated that cytologic changes of LSIL are usually limited to “mature” or superficial-type of cells and the cells occur in sheets and in singles.

- Nuclear enlargement more than three times the size of the nucleus of a normal intermediate cell nuclei resulting in a slightly higher nuclear cytoplasmic ratio.

- Binucleation and multinucleation are common.

- Chromatin is coarsely granular and the nuclear membrane is mildly irregular with inconspicuous nucleoli.

- A markedly delineated clear perinuclear zone and a peripheral rim of densely stained cytoplasm constitute the perinuclear cavitation (“koilocytosis”) which is a typical feature.

HISTOPATHOLOGY

Stratification is well preserved with regular orientation of the cells in the upper two thirds of the epithelium. The middle and upper layers are predominantly composed of superficial type and intermediate type cells with mildly reduced cytoplasmic area and slight increase in the nuclear size. Aberrations of nuclear cytology are limited only to the most basal layers of the squamous epithelium.

HIGH GRADE SIL (CIN-2 AND CIN-3)

CYTOLOGY

- Criteria

  - Cytologic changes are seen in the cells that are comparatively smaller and immature in contrast to those seen in LSIL.

  - Cells occur in sheets, in syncytial aggregates or in singles demonstrating hyperchromasia of nuclei along with alterations in nuclear size and shape.

  - There is variable nuclear enlargement and decrease in cytoplasmic area, leading to a markedly increased nuclear/cytoplasmic ratio.

  - Chromatin demonstrates fine or coarse granularity and the nuclear membrane shows prominent grooves or indentations.

  - Nucleoli though usually inconspicuous, may occasionally be seen.

HISTOPATHOLOGY

In CIN 2 stratification of cells is preserved in the upper one third of the epithelium. Cell orientation is disturbed in the lower two thirds of the squamous epithelium.

In CIN 3, cell arrangement is disturbed in all the layers of the epithelium with the cells exhibiting decreased cytoplasmic volume and an increase in nuclear size with variable shapes and also irregular forms.

Carcinoma in situ refers to a lesion replacing the normal surface epithelium with all the layers of the epithelium showing cells exhibiting poorly differentiated or largely undifferentiated cells[21] but invasion is absent.

INVASIVE CANCER OF THE UTERINE CERVIX

CYTOLOGY

- Criteria
    - Cells show poorly defined borders and are arranged in sheets.
    - Nuclei are round to oval nuclei and show irregularly clumped chromatin and macronucleoli.
    - Eosinophilic cytoplasm seen.
    - Tadpole cells and other bizarre forms may be observed.

ATYPICAL ENDOCERVICAL CELLS OF UNDETERMINED SIGNIFICANCE

- Criteria
    - Endocervical cells which lack unequivocal features of malignancy but which show nuclear atypia which is more obvious than that seen in reactive or reparative changes.

Atypical Endocervical Cells: NOS

- Criteria
    - Cells show nuclear crowding and overlapping and arranged in sheets.
    - Nucleus size is of three to five times the size of normal endocervical nuclei with hyperchromasia and prominent nucleoli.
    - There is increased nuclear cytoplasmic ratio inspite of the abundant cytoplasm.

Atypical Endocervical Cells, Favor Neoplastic

- Cell morphology falls just short of a diagnosis of in situ or invasive endocervical adenocarcinoma.
- Criteria
    - Abnormal cells in sheets and strips with nuclear crowding.
    - Nucleus is large and hyperchromatic with few mitotic figures.
    - The amount of cytoplasm is diminished, cell borders are poorly defined and there is increased nuclear cytoplasmic ratios.

Endocervical adenocarcinoma in situ

- Friedell and McKay were the first to use the term adenocarcinoma-in-situ (AIS), to refer to the preinvasive lesions of cervical adenocarcinoma which failed to demonstrate invasion.

- Criteria

  - Cells occur in strips, sheets, rosettes and clusters with nuclei showing overlapping and crowding and the normal honeycomb pattern is lost.
  - Cells exhibit a feathering pattern with the cytoplasmic tags and nuclei protruding from the periphery with palisading nuclei.
  - Nuclei show oval to elongated shape and stratification with coarsely granular chromatin and inconspicuous nucleoli.
  - Nuclear/cytoplasmic ratios are increased; the quantity of cytoplasm and mucin are reduced.
  - Background is generally clean (no tumor diathesis).

HISTOPATHOLOGY:

AIS refers to the presence of endocervical glands showing lining by columnar epithelial cells which demonstrate atypia but where there is no invasion.

Nuclei are cigar-shaped and elongated and appear hyperchromatic with chromatin showing coarse granularity.

Intracellular mucin and cytoplasm are decreased resulting in an increased nuclear : cytoplasmic ratio.

Two histological types were described by Ostor et al[35]: typical endocervical and intestinal type.

Endocervical Adenocarcinoma

- Cytologic criteria overlap those outlined for AIS, but with features of invasion.

- Criteria

  - Cells are dispersed in singles, two or three dimensional sheets, or syncytial aggregates and clusters.

  - Nuclei are large and pleomorphic with irregular clumps of chromatin, irregular nuclear membrane some showing macronucleoli.

  - The background is necrotic showing tumor diathesis.

HISTOPATHOLOGY:

- Characterised by endocervical glands showing atypical columnar cell lining which are similar to the cells of AIS but demonstrate invasion.

ACOG (2009) Screening Guidelines[36]

- Screening should begin at 21 years of age irrespective of onset of sexual activity.
- Women who are more than 30 years in a monogamous relationship: Can be screened every 3 years when BOTH prior Pap smear and HPV testing for high risk types are negative.
- Women who are more than 30 years with 3 consecutive negative Pap smears AND no risk factors: Can be screened every 3 years.
- Annual screen or at more frequent intervals can be done if high-risk factors such as positive HIV status, history of DES exposure, prior history of cervical dysplasia, or cancer cervix.
- Both liquid-based cytology and conventional Pap smear are acceptable for screening.
- Routine screening may be discontinued in those with a history of total hysterectomy for benign indications and no prior dysplastic changes.

ADVANTAGES OF PAP SMEAR

- No injury to tissue is produced allowing frequent sampling to know the progress of the disease or regression of the lesion.

- Smears cover a wider surface area than that sampled in a biopsy.

- Intimate cellular details are more often clearly seen in an isolated cell of the smear because of the minimum shrinkage and distortion in such cells.
- Special stains can always be used as they are used in tissue sections.
- Changes due to infection and irradiation are easily evaluated.

LIMITATIONS OF PAP SMEAR

- ❖ The interpretation of the morphological cellular changes is subjective.
- ❖ The cytologic diagnosis is not always final. It must often be confirmed by histopathology.
- ❖ The cytologist bases the diagnosis on the study of minute cellular details, while the histopathologist mainly examines the tissue pattern.
- ❖ The interrelation and arrangement of the cells cannot be established.
- ❖ The relation of the cells to the supporting stroma which is important in the diagnosis of an invasive carcinoma cannot be determined by cytology.
- ❖ The size and the location of the lesion cannot be appreciated by cytology.
- ❖ The exfoliated cells may not represent the true nature of the lesion.

- Poorly differentiated cells for example are the only cells exfoliating from a neoplasm with mixed components.

- The screening of a smear can be time consuming and often the nature of the lesion is not obvious as in a histopathological section.

LIQUID BASED CYTOLOGY:

Though Pap smear had emerged as one of the efficient cancer screening programs that had been introduced, conventional Pap smear also had marked disadvantages which resulted in a higher number of false negatives[37.]

These limitations were mainly to two factors: errors in screening and errors in sampling/preparation.

Moreover, it was obvious that the main hindrance to computerised imaging was the poor nature of the cytological preparation as is the case in conventional cytology.

In order to improve increase the consistency and reliability of the Pap smear, LBC was designed to produce a sample that was fully representative of the material removed, and potentially easier to screen.

THIN PREP and SUREPATH

- These are the first attempted liquid based cytology methods, both of them being FDA approved.

- Clinical trials which were conducted with ThinPrep smears revealed an increase in disease detection[38,39].
- Colgan TJ et al[40] studied the advantages of Surepath, another liquid based cytology in a cancer screening programme at Ontario.
- The ThinPrep and the Surepath Pap tests brought about a breakthrough in Pap smear testing by increasing the number of adequate specimen and improving the disease detection rate.
- Preparation of slides involves four steps:

1. Collection of sample:

This is done with a Cervex brush, the tip of which is broken and immersed into a preservative fluid which is ethanol based, hence preserving almost 100% of the sample collected and thereby avoiding any artefacts due to air drying.

2. Process of cell enrichment

Processing of samples is done in batches at the laboratory. The process of cell enrichment utilizes centrifugation and gravity dispersion in order to get rid of the blood, inflammation, mucus and other debris which may obscure the diagnostic material.

3. Automated transfer of cells to slide

The slide processor makes an uniformly dispersed preparation which contains an increased concentration of the representative cells.

These samples are then loaded onto the system thereby facilitating faster screening.

4. **Staining which is completely automated**

After formation of a thin uniform layer over the slide, the process is continued by the Slide Processor utilizing the Hematoxylin and EA/OG stains on-board.

LIQUIPREP™:

- The first attempted liquid-based pap smear preparations utilized plastic devices, automated equipment, vacuums and filters. Hence, these methods were available at an increased cost per slide.
- Maksem JA et al proposed an alternative method of LBC using a metastable alcoholic gel[41].
- Liqui-PrepTM which was put forward by the LGM International, USA) is considered to be a liquid-based pap smear of second generation. Its advantage lies in that the costlier instruments utilized for the first generation tests were not necessary, hence resulting in a method which is simpler to perform and available at a comparatively lower cost for screening of cervical cancer.

STEPS IN PREPARATION OF LIQUIPREP™ SLIDES:

1. Collection of sample with a Cervex brush, the tip of which is detached and put into a preservative fluid which is alcohol based.

2. Cleaning solution added if necessary and centrifugation of the sample is done at 1000g for 10 minutes.
3. Addition of a proportional quantity of cell base reagent for resuspension, following which smears are made using the suspended sample in the form of a circle of 1.5 cm diameter.

INTERPRETATION:

The LP slides consisted of cells spread in a monolayer for a circle of about 1.5 cm diameter, thereby presenting enhanced clarity. Visualization is even more better because of considerably reduced blood and mucus but preserving the leukocytes and thereby a less obscuring effect[42].

MORPHOLOGY IN LBC SMEARS:

Prompt fixation leads to good preservation resulting in clarity of chromatin.

Cells appear slightly smaller due to rounding up effect of fixation in liquid.

Clarity of nuclear features helpful in diagnosing dyskaryosis.

Cells with low grade dyskaryosis (koilocytosis) are easily seen.

Severe dyskaryosis often presents as dispersed single cells.

ADEQUACY:

Bethesda- 5000 cells.

INADEQUACY:

- Before the laboratory: Cervix not fully visualised and sampled, vial broken and leaked or no brush in vial.
- No endocervical cells: Cause of inadequacy in women treated for CGIN or CIN3 with endocervical margins involved.
- Obscured by blood or polymorphs: Extremely rare occurrence on LBC
- Contamination: Use of inappropriate lubricant
- Inadequate cellularity: Thresholds not yet established

ADVANTAGES OF LIQUIPREP TM

- Settakorn J[43] et al proposed that LiquipreqTM offers a considerably low cost compared to the first generation LBC.
- Decreased chance of inadequacy of smear.
- Smear less obscured by inflammatory cells and blood.
- Clarity of nuclear chromatin.
- Squamous cell abnormalities brought out better.

LIMITATIONS OF LIQUIPREP TM

- Higher cost compared to conventional smear.
- Experienced cytologist needed for interpretation.
- Storage of vials may be problematic.
- Diagnosis of glandular abnormalities decreased.

AUTOMATION IN SCREENING

- Since manual screening was tedious and habituating, automated screening methods were introduced.
- Earlier methods were not consistently able to process conventional pap smears in view of the varying thickness and overlapping of nuclei.
- Recent advances in liquid based cytology and the advent of more sophisticated algorithms have resulted in the dream of automated screening come true.

PAPNET

- It is a computer processing system driven by neural network used for screening conventional pap smears.
- According to Mango,L.J. et al[44], this system relies on the ability of the human brain to learn rather than on rules and hence is sensitive in recognising a large number of patterns.

- The computer reviews and selects suspicious cells, that are displayed in 400x magnified fields and 128 video images, alongside the corresponding location on the grid for opinion of an experienced cytologist.
- In a trial by Koss L.G. et al[45] which involved the analysis of 9666 negative pap smears which were manually reported as negative, Papnet was able to identify 464 (4.8%) abnormal smears. This constituted a 30% increased detection rate than the average detection rate of 12.7%.
- The time taken for screening by Papnet was considerably reduced (approximately ***3*** vs. 10 minutes).

AUTOPAP SYSTEM

- An image processor is used to systematically scan the slide following which the images are run through a list of algorithms for interpretation and final impression.
- Clinical trials by Wilbur,D.C.[46] et al showed that when the Autopap system was used for rescreening, there was a five-fold improvement over manual screening.

THIN PREP IMAGING SYSTEM:

This system got the FDA approval in 2003. The ThinPrep Imager scans the ThinPrep slide and picks up suspicious areas for further opinion of an experienced cytologist.

- A DNA stain stains the nuclei of the cervical cells present in the smear. Suspicious cells are those with high content of molecular DNA, and are enlarged with irregular shapes. The nuclei of these suspicious cells show more intense staining.
- The ThinPrep Imaging System scans every smear and identifies 22 fields of interest with respect to the DNA content of cells.

- The cytologist reviews these 22 fields of interest and reports "no intraepithelial lesion" if all fields appear normal. If the cytotechnologist finds suspicious cells, then the entire slide is reviewed by a pathologist.

BD FOCAL POINT™ GS IMAGING SYSTEM:

- The BD FocalPoint™ GS Imaging System is a computer-aided imaging instrument equipped with an automated microscope for initial screening for abnormal cells in cervical cytology samples.

- This system scans the slide identifying up to 10 fields of interest which are viewed by the cytotechnologist using the review microscope. If there are no abnormal cells, the slide is considered negative but if abnormal cells are found, the whole slide is reviewed.

ADVANTAGES OF AUTOMATED IMAGING:

- Helps reduce human error and thereby false negative test results.
- Fivefold increased detection rates of abnormal cells.
- Time taken for screening considerably reduced.

DISADVANTAGES OF AUTOMATED SCREENING:

- Early computer classification schemes were not able to deal with the numerous morphologies presenting as various degrees of abnormal findings.
- Are not able to consistently process conventional pap smears owing to varying thickness and nuclear overlapping.

HPV TESTING:

- A definitive diagnosis can be made only by the direct detection of HPV DNA by in situ hybridization, by nucleic acid amplification via polymerase chain reaction (PCR), or by hybrid capture (HC) techniques.
- Among the two, Hybrid capture is the more frequently used. It utilises RNA probes that are complementary to the13 high-risk and 5 low-risk HPV types.
- RNA-DNA hybrids are prepared by denaturing the HPV-DNA in the specimen and hybridising to the RNA probes, which are then captured on to microtiter plates containing monoclonal antibodies.

Alkaline phosphatase conjugated second monoclonal antibody is allowed to react with the captured hybrids and then a chemoluminescent substrate is added.

- The chemoluminescent substrate is cleaved by the alkaline phosphatase conjugate and the light emitted is detected by a luminometer. The intensity of light emitted is in proportion to the amount of HPV-DNA.
- This test can detect concentrations as low as 0.2pg/mL of HPV DNA in the sample .
- The results from trials conducted by Hybrid Capture, Digene Corp. which involved around 23, 000 women showed the sensitivity for HPV testing was 90% for HSIL whereas it was only 67% for conventional pap smear[47].

P16-INK4A:

- P16-INK4A is a kinase inhibitor which is cyclin-dependent and shows overexpression in those cell lines in which the retinoblas-toma protein RB has been inactivated by E7 protein product of the high risk HPV.
- P16-INK4A can be identified by immunohistochemistry or ELISA, and thus is a potential marker which can be used for screening for cancer cervix.

- A study conducted in Italy involving 24,661 patients showed that the sensitivity of P16-INK4A to diagnose HSIL was 88% and the specificity was 61%[48].

CERVICAL BIOPSY

In this procedure cervical tissue is removed from the cervix to detect precursors of cancer or invasive cervical carcinoma. Cervical biopsies are of various types. In addition to removal of the cervical tissue for diagnosis, few biopsies may also excise completely the abnormal tissue and thereby used therapeutically for cancer precursors.

Types of cervical biopsies:

***Punch biopsy** - This procedure removes a small bit of cervical tissue with the aid of a punch biopsy forceps. Various areas are sampled.

***Cone biopsy or conization** - A scalpel or LASER is used to excise a huge amount of cervical tissue in the shape of a cone from the cervix.

***LLETZ**

- The gynaecologist uses electric current of varied power settings passed via a wire loop to excise tissue from the cervix.

- The cervical transformation zone along with the lesion are excised to a depth of 8 mm, and extending 4-5 mm beyond the lesion.

- Low cost, high success rate, and ease of use are the advantages of this procedure.

- Complications of this procedure are infection, hemorrhage, damage to the cervical stroma resulting in cervical stenosis or incompetence. The LLETZ does not seem to affect fertility[49].

MATERIALS AND METHODS

MATERIALS AND METHODS

This comparative analysis was a prospective study which was conducted at Institute of Social Obstetrics and Govt. Kasturba Gandhi hospital, Chennai, attached to Madras Medical College, from June 2011 to June 2012.

This study involved women [n=200] who attended the colposcopy out patient department, who were screened for cancer cervix using visual inspection with acetic acid and Lugol's iodine, conventional Pap smear cytology and liquid based cytology.

INCLUSION CRITERIA:

1. Women attending the colposcopy out patient department with symptoms of white discharge per vagina, abnormal uterine bleeding, postcoital bleeding, pruritis vulva and those with family history of gynaecological malignancy.

2. Women who are sexually active or on oral contraceptives.

3. Non pregnant women.

4. Both nullipara and multipara.

EXCLUSION CRITERIA:

1. Pregnant women.

2. Menstruating women.

3. History of hysterectomy.

4. Sexual intercourse with spermicidal jelly, douches/tampons 24 hours prior to pap smear examination.

VISUAL INSPECTION WITH ACETIC ACID (VIA) & WITH LUGOL'S IODINE (VILI)

THE EXAMINATION:

- The procedure is carefully explained to the patients, they are made comfortable and privacy ensured.
- The patient is placed in the lithotomy position.
- Good visualization ensured.
- Any abnormal findings in the external genitalia are recorded.
- Cusco's speculum is inserted into the vagina so that the cervix is clearly visualised.
- The discharge or mucus is wiped by means of a cotton swab wet with normal saline.
- The external appearance of cervix is recorded.

- ❖ Cervix washed using freshly prepared 5% acetic acid using a syringe. (Alternatively can be applied with cotton swab).
- ❖ The cervix observed for acetowhite areas after waiting for a minute.
- ❖ Lugol's Iodine applied by means of a cotton swab or syringe.
- ❖ The cervix inspected for iodine uptake areas & non uptake areas.
- ❖ Findings were recorded.

CHARATERSTICS OF VIA / VILI –POSITIVE CASES

(**A)Low grade lesion**

Detection of any acetowhite area – VIA

Detection of any non iodine uptake areas – VILI.

(B) High Grade Lesion

Presence of opaque acetowhite patches which appear well circumscribed, abutting the squamocolumnar junction.

Detection of thick, dense, saffron yellow or mustard yellow iodine non-uptake lesions in the tranformation zone around the squamocolumnar juction.

CONVENTIONAL PAP SMEAR

Timing:

- Smears are not collected during the menstrual periods.
- The patient should not have intravaginal medications / douches 48 hrs before the test.
- Patient should not have intercourse the previous night.

Precautions:

- Lubricants of all types avoided.
- Vaginal examination to be done only after taking smear.

Method:

- Combination of Ayre's Spatula and Endocervical brush has proved to give better results.
- The patient is put in lithotomy position.
- Visualisation of cervix by Cusco's speculum.
- The spatula placed at the level of cervical os and rotated through 360° circle around the os ensuring that the spatula is in contact with the ectocervix.
- Optimal sample is taken and a smear is made on a clean slide.
- Endocervical brush is inserted into the os and rotated through 180°.

- The angle of rotation should be parallel to the endocervical canal.
- The sample is rolled on to the slide in the direction opposite to which it was rolled for collecting the sample.
- The smear quality is better if the spatula is used first following which endocervical brush is used thereby making obscuring of smears by blood less likely.
- The slide is fixed with 95% ethyl alcohol – Fixative.

STEPS IN PREPARATION OF LIQUIPREPTM SLIDES:

Collection of sample: The sample was taken with the help of a Rover Cervex brush, the tip of which was broken and dropped into the alcohol based LP preservative fluid.

Concentration of the sample: The vial along with the tip of the brush was shaken forcefully with the help of a vortex for about 10 seconds. The contents of the vial were emptied into a 15 ml centrifuge tube. Samples that contained mucus or blood were cleared with 4 ml of cleaning solution. Centrifugation was done for approximately1000g for 10 minutes.

Preparation of the slides: The supernatant present following centrifugation was poured off. Cell base reagent was added to the sample in an amount proportional to the cell pellet formed, in accordance to the instructions by the manufacturer. A vortex was used for 10 seconds to

resuspend the cell pellet. Then about 50 microlitres of the suspended cell pellet was pipetted onto a clean slide in the form of a circle of 1.5 cm diameter following which the slides are air-dried and stained by routine Pap stain.

PAP STANING:

MATERIALS REQUIRED:

- Harris hematoxylin was prepared using potassium alum and mercuric oxide and filtered into a dark bottle for storage. The working solution was replaced every 1 to 3 weeks, depending on the number of slides being stained.
- OG 6

  Orange G 1.0% solution in 95% Alcohol - 100ml.

  Phosphotungstic acid - 0.015gm.

- EA 36

  Light green SF yellowish - 0.14% in 95% alcohol - 45ml.

  Bismark brown Y- 0.5% in 95% Alcohol - 10ml.

  Eosin yellow - 0.55% in 95% alcohol - 45ml.

  Phosphotungstic acid - 0.2 gm.

  Lithium carbonate, saturated aqueous solution - 1 drop.

PROCEDURE

1. Slides were transferred directly from the fixative, without drying, to 95% alcohol, and brought down through 70 and 50% alcohols to distilled water.

2. Slides were stained in Harris hematoxylin for 5 minutes.

3. Gently rinsed briefly in distilled water.

4. They were dipped in 0.25%Hcl in 50% ethanol (acid alcohol) about six times for 20 seconds.

5. Placed in running tap water for 6 minutes.

6. They were rinsed in distilled water and run through 70%, 80% to 95% alcohol.

7. And stained in OG 6 for 3 minutes.

8. The slides are then rinsed in 95% alcohol- 2 changes.

9. Stained in EA 36 for 3 minutes.

10. Rinsed in 95% alcohol- 3changes.

11. Dehydrated in absolute alcohol, followed by equal parts of absolute alcohol and xylol, cleared in xylol and mounted. The

smears were analyzed and the cellular details were evaluated under a light microscope.

PAP REPORTING IN THE HOSPITAL

1. Negative for SIL
2. Cervicitis
3. Atypical cells of undetermined significance
4. Atypical cells cannot exclude HSIL
5. Low grade SIL
6. High grade SIL
7. Invasive carcinoma

CERVICAL BIOPSY

For 77 cases (65 cases which showed abnormal results on either VIA/VILI or pap smear and 12 normal cases), either punch biopsy or LLETZ biopsy was taken and sent for histopathological report. The biopsy reporting in our hospital is as follows.

1. No major lesion detected
2. Cervicitis
3. Mild Dysplasia-CIN 1
4. Moderate dysplasia-CIN 2
5. Severe dysplasia-CIN 3,

6. Carcinoma in situ

7. Invasive Carcinoma

COMPARATIVE ANALYSIS:

The information collected regarding all the selected cases were recorded in a Master Chart.

Sensitivity, specificity, accuracy, positive predictive value and negative predictive values, percentage of false positives and false negatives were calculated using the following formulae and taking HPE findings as the Gold standard.

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive + false negative}} \times 100$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{False positive + true negative}} \times 100$$

$$\text{Positive predictive value} = \frac{\text{True positive}}{\text{True positive + False positive}} \times 100$$

$$\text{Negative predictive value} = \frac{\text{True negative}}{\text{True negative + False negative}} \times 100$$

$$\text{Percentage of false positives} = \frac{\text{False positive}}{\text{False positive + True negative}} \times 100$$

$$\text{Percentage of false negatives} = \frac{\text{False negative}}{\text{False negative + True positive}} \times 100$$

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

The study was conducted at Institute of Social Obstetrics and Govt. Kasturba Gandhi Hospital for Women & Children, Chennai, attached to Madras Medical College during the period June 2011 – June 2012.

200 Patients were included in the study group and the outcome analysed using various parameters. The results were subjected to statistical analysis.

- Sample size – 200.
- Visual Inspection with Acetic Acid (VIA), done in all 200 patients.
- Visual Inspection with Lugol's Iodine (VILI) done in all 200 patients .
- Conventional Pap smear cytology and liquid based cytology was done in all 200 cases.
- Those cases showing VIA/VILI Positive (or) cytology positive were subjected to cervical biopsy.
- For 12 cases which were negative on Pap smear and also on VIA/VILI, biopsy was done (as control)

I. CHARACTERISTICS OF THE STUDY GROUP:

70 patients (35%) enrolled in the study belonged to the age group of 31-40 years (Table 1 and Chart 1).

TABLE 1

AGE DISTRIBUTION

n=200

AGE (YEARS)	≤20	21-30	31-40	41-50	≥51
FREQUENCY	2	39	70	60	29
PERCENT	1%	19.5%	35%	30%	14.5%

37% of the patients were of socioeconomic grade 4 while 33.5% of the patients were of socioeconomic group 5 (Table 2 and Chart 2).

TABLE 2

DISTRIBUTION OF SOCIOECONOMIC GROUP IN THE STUDY GROUP

n=200

GRADE	2	3	4	5
FREQUENCY	12	47	74	67
PERCENT	6%	23.5%	37%	33.5%

Among the study group, 82% of the patients attained menarche at 13-14 years of age (Table 3 and Chart 3).

TABLE 3

DISTRIBUTION OF AGE AT MENARCHE IN THE STUDY GROUP

n=200

AGE (YEARS)	≤12	13-14	15-16
FREQUENCY	26	164	10
PERCENT	13%	82%	5%

Among the 200 patients, 73% of the marriages in the study group were around 15-20 years (Table 4).

TABLE 4

DISTRIBUTION OF AGE AT MARRIAGE IN THE STUDY GROUP

n=200

AGE (YEARS)	15-20	21-25	26-30	≥31
FREQUENCY	146	46	4	4
PERCENT	73%	23%	2%	2%

Out of the 200 patients, 93 patients (46.5%) in this study group were of parity 2 and 57 patients (28.5%) were of parity 3(Table 5 and Chart 4).

TABLE 5

DISTRIBUTION OF STUDY GROUP ACCORDING TO PARITY

n=200

PARITY	0	1	2	3	≥4
FREQUENCY	6	18	93	57	26
PERCENT	3%	9%	46.5%	28.5%	13%

The most common presenting symptom in the study group was white discharge per vaginum (63%) followed by abnormal uterine bleeding (19.5%) (Table 6 and Chart 5). White discharge per vagina was also the commonest presenting symptom in patient who showed dysplasia on biopsy.

TABLE 6

DISTRIBUTION OF SYMPTOMS AMONG THE STUDY GROUP

n=200

SYMPTOMS	FREQUENCY	PERCENT
WHITE DISCHARGE	126	63%
AUB	39	19.5%
POSTCOITAL BLEED	4	2%
PAIN ABDOMEN	24	12%
PRURITIS VULVA	7	3.5%

RESULTS OBTAINED BY SCREENING METHODS

FINDINGS IN VIA/VILI

VIA/VILI was positive in 68 cases (34%) and 132 cases (66%) showed negative results (Table 7 and Chart 6).

TABLE 7

DISTRIBUTION OF VIA/VILI POSITIVE CASES IN THE STUDY GROUP

VIA/VILI POSITIVE	68 CASES	34%
VIA/VILI NEGATIVE	132 CASES	66%

In the study group majority of the patients who were VIA/VILI positive belonged to 31-40 years age group (39.7%) and 41-50 years (27.9%) –(Table 8 and Chart 7)

TABLE 8

AGEWISE DISTRIBUTION OF VIA/VILI POSITIVE CASES

n=68 VIA/VILI positive cases

AGE	21-30	31-40	41-50	≥51
VIA/VILI POSITIVE	8	27	19	14
PERCENT	11.8%	39.7%	27.9%	20.6%

36.8% of the patients who were VIA/VILI positive were of socioeconomic grade 4 and 30.8% of the patients were of grade 5 (Table 9 and Chart 8).

TABLE 9

VIA/VILI RESULTS- SOCIOECONOMIC STATUSWISE

n=68 VIA/VILI positive cases

SOCIOECONOMIC STATUS	2	3	4	5
FREQUENCY	5	17	25	21
PERCENT	7.4%	25%	36.8%	30.8%

CYTOLOGY REPORTS

Pap smear report was inadequate in 7 patients (3.5%), normal in 20 patients (10%), atrophic smear in 8 patients (4%), Cervicitis in 115 patients (57.5%), ASCUS in 2 patients (1%), LSIL in 11 patients (5.5%), HSIL in 18% (9%), SCC in 17 patients (8.5%) and adenocarcinoma in 2 patients (1%)– (Table 10 and Chart 9).

TABLE 10

CONVENTIONAL PAP SMEAR RESULTS

FINDINGS	NUMBER OF CASES	PERCENT
INADEQUATE	7	3.5%
NORMAL	20	10%
ATROPHIC	8	4%
CERVICITIS	115	57.5%
ASCUS	2	1%
LSIL	11	5.5%
HSIL	18	9%
SCC	17	8.5%
ADENOCARCINOMA	2	1%

LBC report was inadequate in 3 patients (1.5%), normal in 20 patients (10%), atrophic smear in 9 patients (4.5%), Cervicitis in 113 patients (56.5%), LSIL in 15 patients (7.5%), HSIL in 21% (10.5%), SCC in 17 patients (8.5%) and adenocarcinoma in 2 patients (1%)– (Table 11 and Chart 10).

TABLE 11

LBC RESULTS

FINDINGS	NUMBER OF CASES	PERCENT
INADEQUATE	3	1.5%
NORMAL	20	10%
ATROPHIC	9	4.5%
CERVICITIS	113	56.5%
ASCUS	-	0%
LSIL	15	7.5%
HSIL	21	10.5%
SCC	17	8.5%
ADENOCARCINOMA	2	1%

Biopsy was reported as cervicitis in 22 cases (28.5%), CIN 1 in 16 cases (20.8%), CIN 2 in 14 cases (18.2%), CIN 3 in 6 cases (7.8%), carcinoma in situ with focal microinvasion in 1 case (1.3%), SCC in 16

cases (20.8%) and adenocarcinoma in 2 cases (2.6%)– (Table 12 and Chart 11).

TABLE 12

BIOPSY FINDINGS

- Biopsy done in 77 cases.
- 65 cases either VIA/VILI or cytology positive.
- 12 cases VIA/VILI negative and also negative on both conventional pap and LBC.

FINDINGS	NUMBER OF CASES	PERCENT
CERVICITIS	22	28.5%
CIN 1	16	20.8%
CIN 2	14	18.2%
CIN3	6	7.8%
CIS	1	1.3%
SCC	16	20.8%
ADENOCARCINOMA	2	2.6%

The most common age group of CIN is 31-40 years whereas invasive carcinoma is common above the age group of 50 years (Table 13 and Chart 12).

TABLE 13

AGEWISE DISTRIBUTION OF BIOPSY RESULTS

BIOPSY RESULTS	≤20	21-30	31-40	41-50	≥50
CERVICITIS(22)	-	1	11	6	4
CIN 1(16)	-	2	7	5	2
CIN 2(14)	-	2	7	5	-
CIN 3(6)	-	-	5	1	-
CIS(1)	-	-	-	-	1
SCC(16)	-	-	2	3	11
ADENOCARCINOMA(2)	-	-	1	-	1

COMPARISON STUDIES

28 low grade lesions on colposcopy were reported as normal- 1, inflammatory- 16, ASCUS- 2, LSIL- 8 and HSIL-1. 21 high grade lesions on colpocopy were reported as inflammatory- 1, inadequate- 3 and HSIL-17. 19 cases of invasive carcinoma turned out to be 17 cases of SCC and 2 cases of adenocarcinoma. 132 negative cases on colposcopy were normal- 19, atrophic- 8,inflammatory- 98, inadequate-4 and LSIL- 3 on pap smear (Table 14 and Chart 13).

TABLE 14

VIA/VILI WITH CONVENTIONAL PAP

VIA/VILI	CONVENTIONAL PAP SMEAR								
	NOR	ATROP	CERVICITIS	INADEQ	ASCUS	LSIL	HSIL	SCC	ADENOCA
LOW GRADE (28)	1		16		2	8	1		
HIGH GRADE (21)			1	3			17		
INVASIVE CA (19)								17	2
NEGATIVE (132)	19	8	98	4		3			

28 low grade lesions were reported as normal-1, inflammatory- 16, LSIL- 10 and HSIL- 1. 21 high grade lesions were reported as inflammatory-1 and HSIL- 20. 19 cases of invasive carcinoma were SCC-17 and adenocarcinoma- 2. 132 negative lesions were reported as normal-19, atrophic- 9, inflammatory- 96, inadequate- 3 and LSIL-5 (Table 15 and Chart 14).

TABLE 15

VIA/VILI WITH LBC

VIA/VILI	LIQUID BASED CYTOLOGY								
	NOR	ATROP	CERVICITIS	INADEQ	ASCUS	LSIL	HSIL	SCC	ADENO CA
LOW GRADE (28)	1		16			10	1		
HIGH GRADE (21)			1				20		
INVASIVE CA(19)								17	2
NEGATIVE (132)	19	9	96	3		5			

20 low grade lesions were reported as cervicitis- 8, CIN I-10 and CIN II- 2. 21 high grade lesions on colposcopy were reported as CIN I- 3, CIN II-12 and CIN III- 6. 17 cases of invasive carcinomas were reported as carcinoma in situ with focal microinvasion- 1, SCC- 16 and adenocarcinoma- 2 on biopsy (Table 16and Chart 15).

TABLE 16

VIA/VILI WITH BIOPSY

VIA/VILI	BIOPSY						
	CERVICITIS	CIN 1	CIN2	CIN 3	CIS	SCC	ADENOCA
LOW GRADE(20)	8	10	2				
HIGH GRADE(21)		3	12	6			
INV CA(19)					1	16	2
NEGATIVE(17)	14	3					

True positive cases- 52

True negative cases- 14

False positive- 8

False negative- 3

TABLE 17

NUMBER OF TRUE POSITIVES, TRUE NEGATIVES, FALSE POSITIVES AND FALSE NEGATIVES ON VIA/VILI

VIA/VILI	BIOPSY	
	Positive	Negative
Positive	52	8
Negative	3	14

Sensitivity=52/55x100=94.55%

Specificity=14/22x100=63.64%

Positive predictive value=52/60x100=86.67%

Negative predictive value=14/17x100=82.35%

Percentage of false positives=8/22x100=36.36%

Percentage of false negatives=3/55x100=5.45%

1 normal smear was reported as cervicitis on biopsy, 22 cases of cervicitis on pap smear were given as cervicitis- 19 and CIN I- 3 on biopsy. 1 atrophic smear was reported as cervicitis. 3 inadequate smears were reported as CIN II- 2 and CIN III- 1. 2 cases of ASCUS were CIN I on biopsy. 11 cases of LSIL were given as CIN I-10 and cervicitis- 1. 18 cases of HSIL turned out to be CIN I- 2, CIN II-11, CIN III-5. 19 cases of invasive carcinoma were reported carcinoma in situ with focal microinvasion- 1, SCC- 16 and adenocarcinoma- 2 on biopsy (Table 18 and Chart 16).

TABLE 18

CONVENTIONAL PAP WITH BIOPSY

CONVENTIONAL PAP SMEAR	BIOPSY						
	CIN 1	CIN 2	CIN 3	CIS	SCC	ADENO CA	CERVICITIS
NORMAL(1)							1
CERVICITIS(22)	3						19
ATROPHIC(1)							1
INADEQ(3)		2	1				
ASCUS(2)	2						
LSIL(11)	10						1
HSIL(18)	2	11	5				
INV CA(19)				1	16	2	

True positives- 49
True negatives- 21
False positive- 1
False negative- 6

TABLE 19

NUMBER OF TRUE POSITIVES, TRUE NEGATIVES, FALSE POSITIVES AND FALSE NEGATIVES ON CONVENTIONAL PAP SMEAR

CONVENTIONAL PAP SMEAR	BIOPSY	
	Positive	Negative
Positive	49	1
Negative	6	21

Sensitivity=49/55x100=89.09%

Specificity=21/22x100=95.45%

Positive predictive value=49/50x100=98%

Negative predictive value=21/27x100=77.78%

Percentage of false positives=4.55%

Percentage of false negatives=10.91%

2 normal smears were reported as cervicitis on biopsy,15 cases of cervicitis on LBC smear were given as cervicitis- 12 and CIN I- 3 on biopsy. 2 atrophic smears were reported as cervicitis. 15 cases of LSIL were given as CIN I-11, CIN II- 1 and cervicitis-3. 21 cases of HSIL turned out to be CIN I- 2, CIN II-13, CIN III-6. 19 cases of invasive carcinoma were reported as carcinoma in situ with focal microinvasion-1, SCC-16 and adenocarcinoma-2 on biopsy(Table 20 and Chart 17).

TABLE 20

LBC WITH BIOPSY

LIQUIPREP TM	BIOPSY						
	CIN 1	CIN 2	CIN 3	CIS	SCC	ADENOCA	CERVICITIS
NORMAL(2)							2
CERVICITIS(15)	3						12
ATROPHIC(2)							2
INADEQ(0)							
ASCUS(0)							
LSIL(15)	11	1					3
HSIL(21)	2	13	6				
INV CA(19)				1	16	2	

True positives- 52

True negatives- 19

False positives- 3

False Negatives- 3

TABLE 21

NUMBER OF TRUE POSITIVES, TRUE NEGATIVES, FALSE POSITIVES AND FALSE NEGATIVES ON LIQUIPREP TM

LIQUID BASED CYTOLOGY	BIOPSY	
	Positive	**Negative**
Positive	52	3
Negative	3	19

Sensitivity=52/55x100=94.55%

Specificity=19/22x100=86.36%

Positive predictive value=52/55x100=94.55%

Negative predictive value=19/22x100=86.36%

Percentage of false positives=13.63%

Percentage of false negatives=5.45%

20 normal smears were reported as normal- 13, cervicitis- 6 and inadequate- 1 on liquid based cytology. 115 inflammatory smears were given as normal-6 cervicitis- 104, inadequate- 1, atrophic- 1 and LSIL-3.8 atrophic smears were reported as inadequate- 1 and atrophic- 7. 7 inadequate smears were reported as normal- 1, cervicitis- 2, atrophic- 1 and HSIL- 3. 2 cases of ASCUS were given as cervicitis- 1 and LSIL-1.11 cases of LSIL and 18 cases of HSIL were concordant on both

conventional Pap and LBC. 17 cases of SCC and 2 cases of adenocarcinoma were reported the same in LBC too (Table 22 and Chart 18).

TABLE 22

CONVENTIONAL PAP WITH LBC

CONVENTIONAL PAP	LIQUIPREP TM							
	NORMAL	CERVICITIS	INADEQUATE	ATROPHIC	LSIL	HSIL	SCC	ADENOCA
NORMAL(20)	13	6	1					
CERVICITIS (115)	6	104	1	1	3			
ATROPHIC(8)			1	7				
INADEQ(7)	1	2		1		3		
ASCUS(2)		1			1			
LSIL(11)					11			
HSIL(18)						18		
SCC(17)							17	
ADENOCA(2)								2

- The percentage of concordance of conventional pap smear with biopsy was 100% for ASCUS, 90.91% for LSIL, 88.89% for HSIL and 100% for invasive carcinoma (Table 23).
- The percentage of concordance of Liquiprep TM pap smear with biopsy was 80% for LSIL, 90.47% for HSIL and 100% for invasive carcinoma (Table 23).

TABLE 23

PERCENTAGE OF CONCORDANT CASES IN CONVENTIONAL PAP AND LIQUIREP TM

	ASCUS	LSIL	HSIL	INVASIVE CARCINOMA
CONVENTIONAL PAP				
TOTAL	2	11	18	19
CONCORDANT	2	10	16	19
%OFAGREEMENT	100%	90.91%	88.89%	100%
LIQUIPREP TM				
TOTAL	-	15	21	19
CONCORDANT	-	12	19	19
%OFAGREEMENT	-	80%	90.47%	100%

Both VIA/VILI and LBC had similar sensitivity rates in the screening of cancer cervix compared to conventional Pap smear. However the specificity and PPV were highest for the conventional Pap smear followed by LBC. Liquiprep TM had the highest negative predictive value (Table 24 and Chart 19 & 20).

TABLE 24

EFFICACY OF VARIOUS SCREENING PROCEDURES

	VIA/VILI	CONVENTIONAL PAP	LIQUIPREP TM
SENSITIVITY	94.55%	89.09%	94.55%
SPECIFICITY	63.64%	95.45%	86.36%
PPV	86.67%	98%	94.55%
NPV	82.35%	77.78%	86.36%
PERCENTAGE O F FALSE POSITIVES	36.36%	4.55%	13.63%
PERCENTAGE OF FALSE NEGATIVES	5.45%	10.91%	5.45%

CHART 1

AGE DISTRIBUTION AMONG THE STUDY GROUP

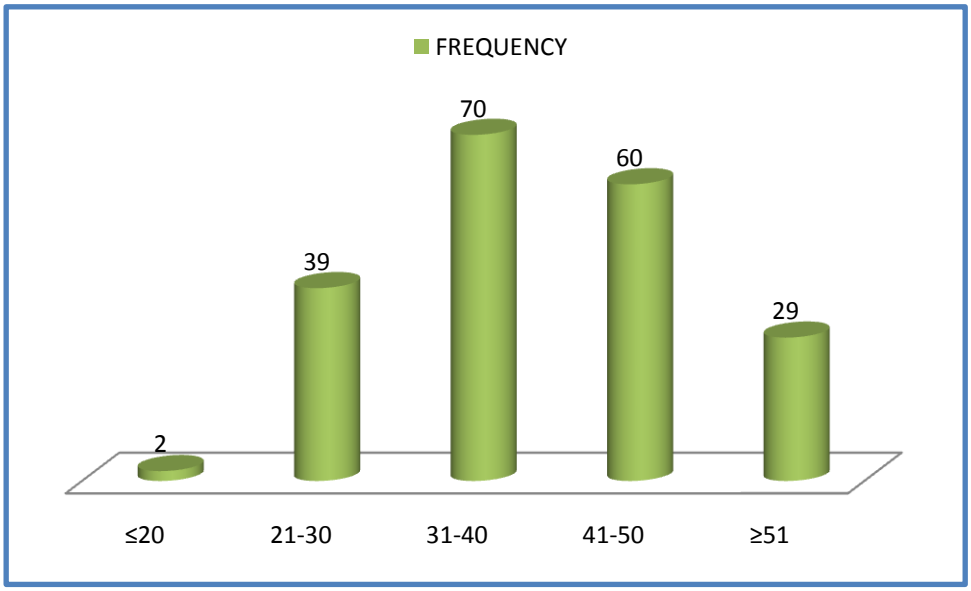


CHART 2

DISTRIBUTION OF SOCIOECONOMIC GROUP IN THE STUDY GROUP

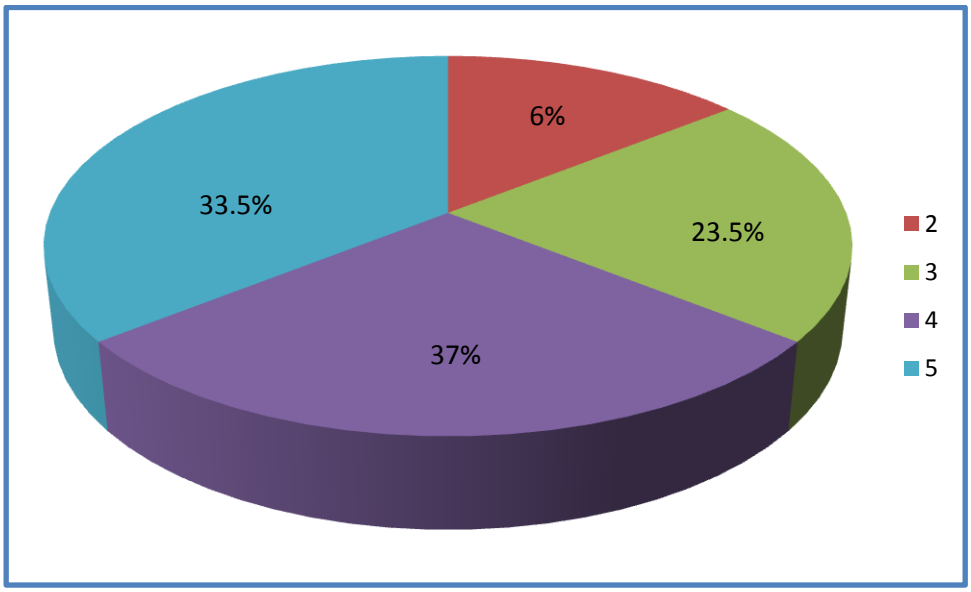


CHART 3

DISTRIBUTION OF AGE AT MENARCHE IN THE STUDY GROUP

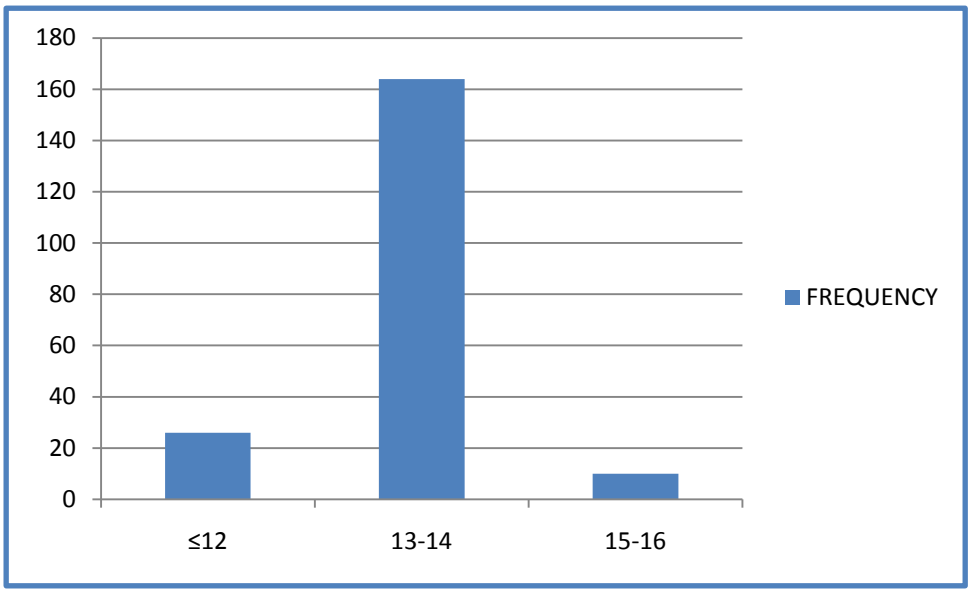


CHART 4

DISTRIBUTION OF STUDY GROUP ACCORDING TO PARITY

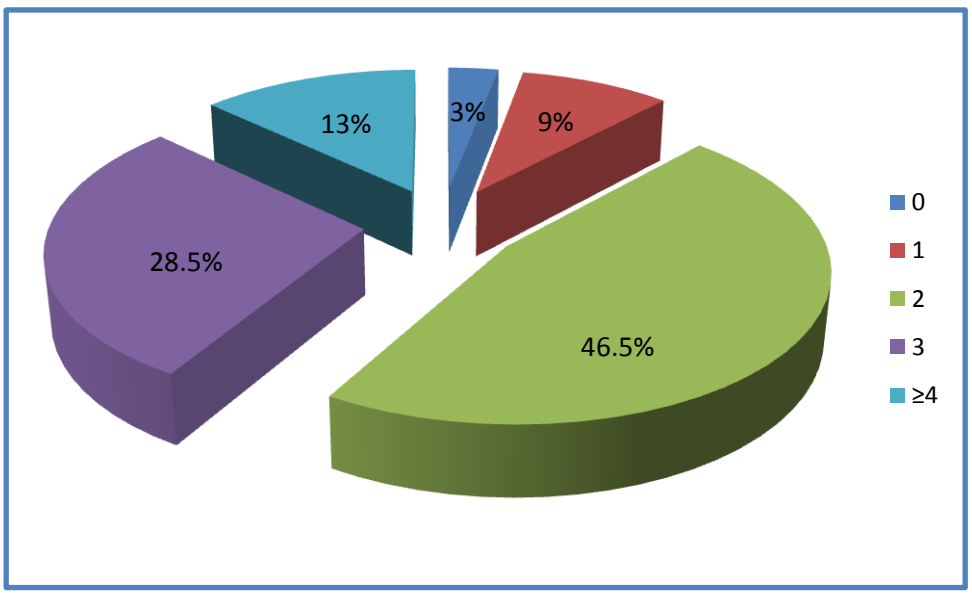


CHART 5

DISTRIBUTION OF SYMPTOMS AMONG THE STUDY GROUP

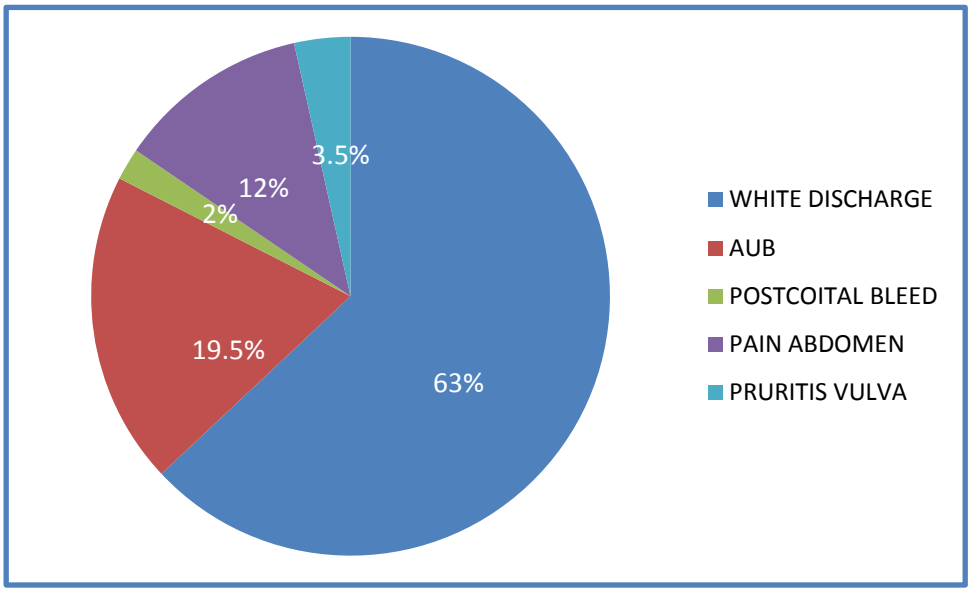


CHART 6

FINDINGS IN VIA/VILI

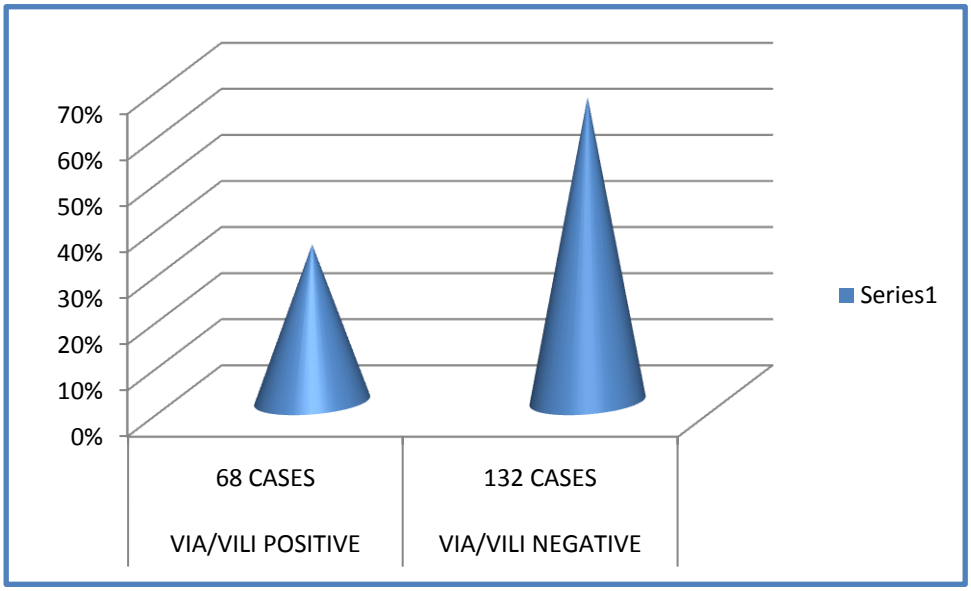


CHART 7

AGEWISE DISTRIBUTION OF VIA/VILI POSITIVE CASES

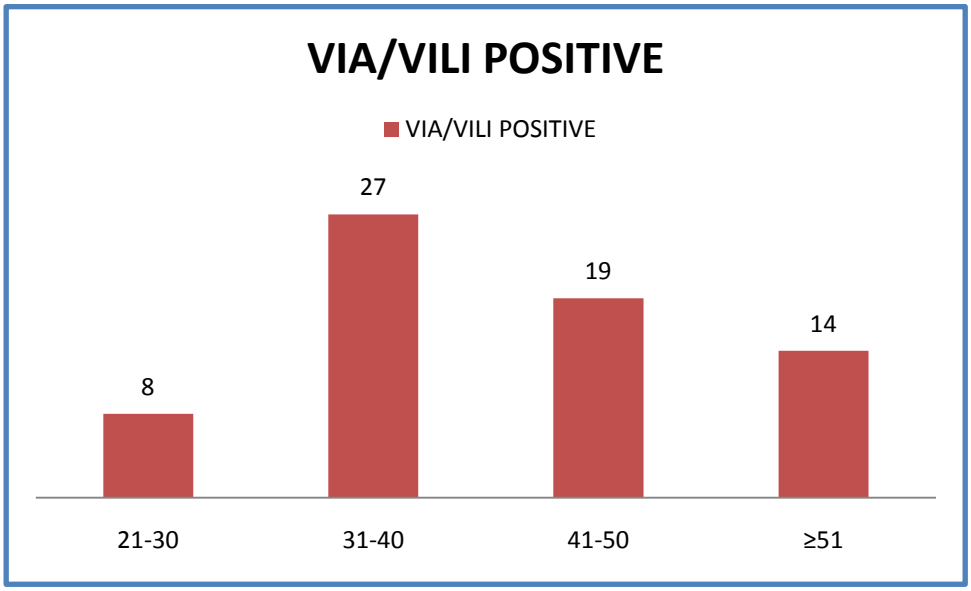


CHART 8

VIA/VILI RESULTS- SOCIOECONOMIC STATUSWISE

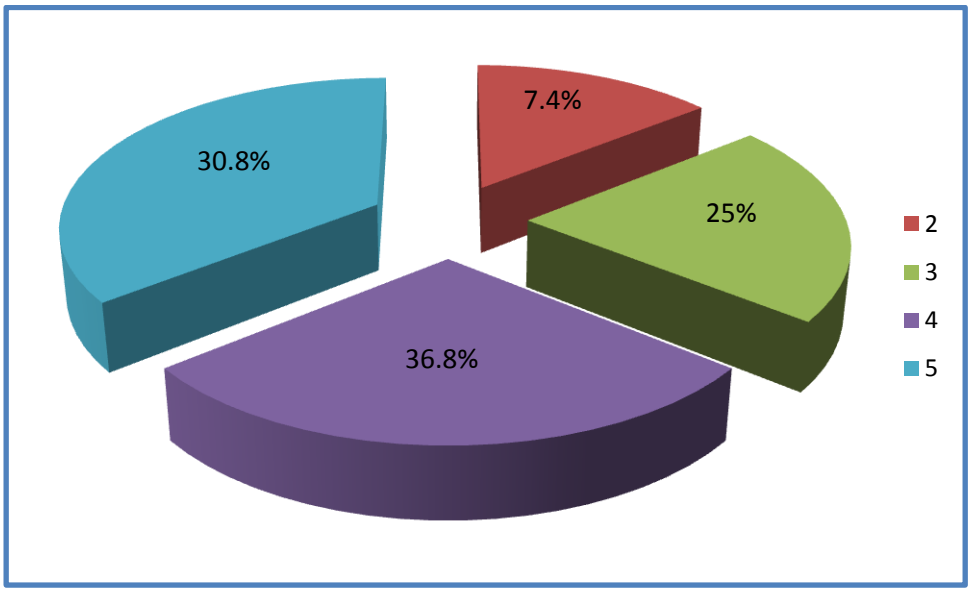


CHART 9

CONVENTIONAL PAP SMEAR RESULTS

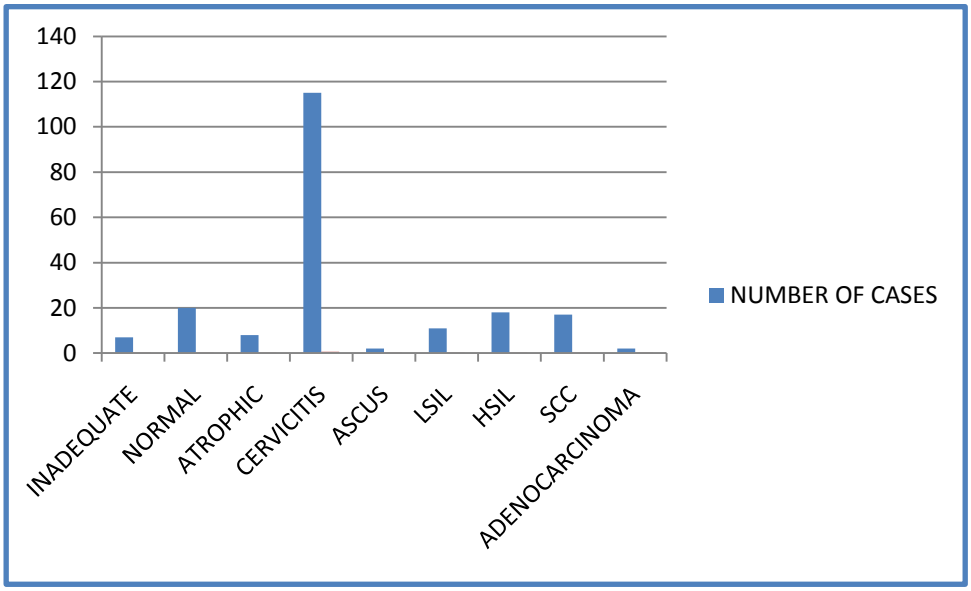


CHART 10

LBC RESULTS

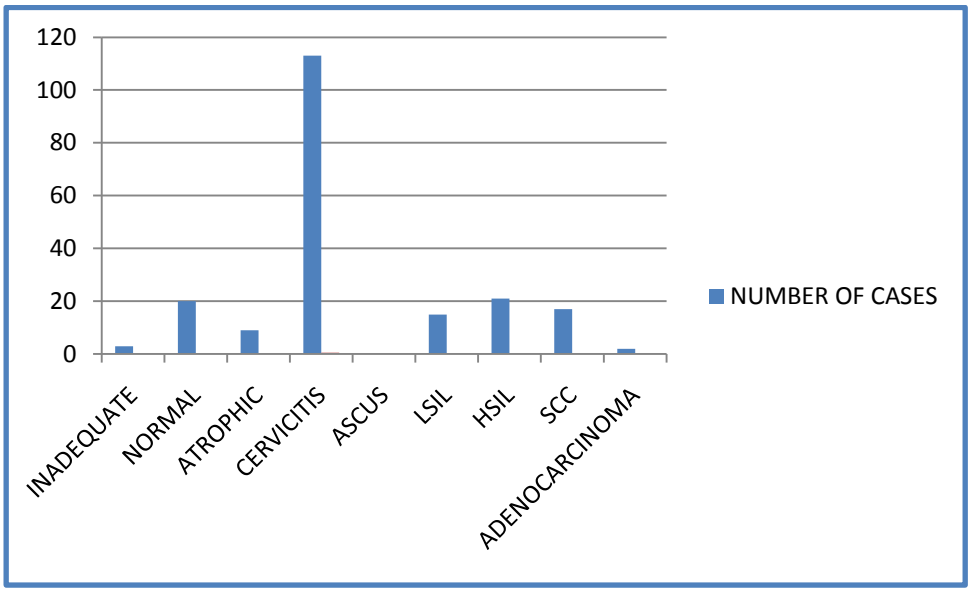


CHART 11

BIOPSY FINDINGS

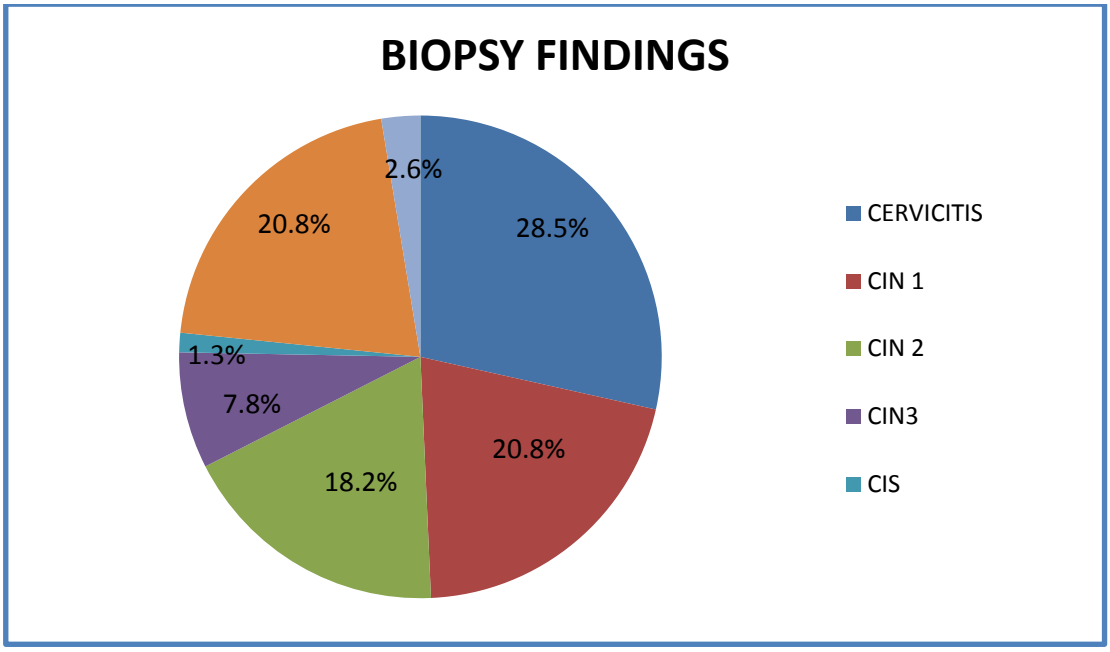


CHART 12

AGEWISE DISTRIBUTION OF BIOPSY FINDINGS

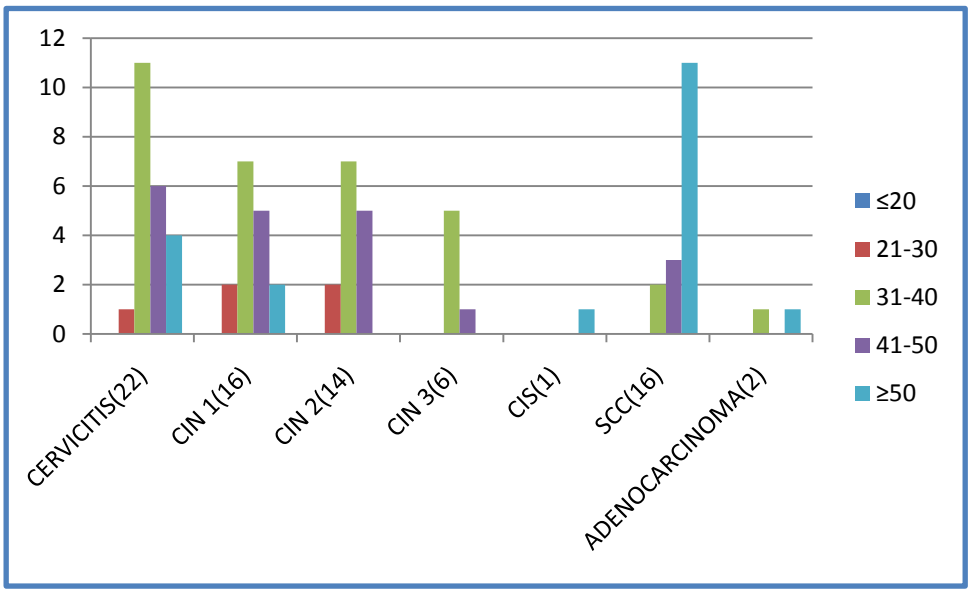


CHART 13

COMPARISON OF VIA/VILI WITH CONVENTIONAL PAP

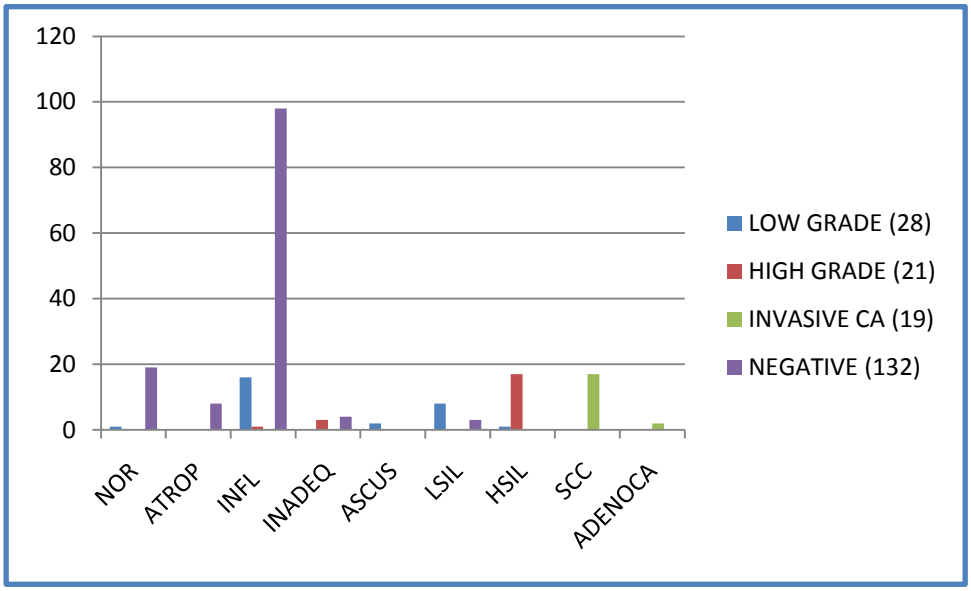


CHART 14

COMPARISON OF VIA/VILI WITH LBC

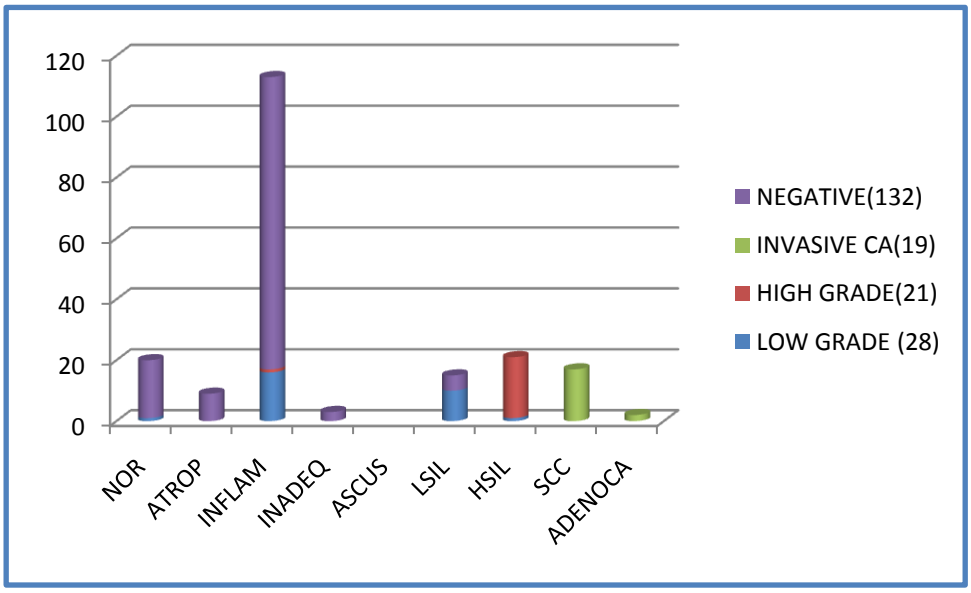


CHART 15

COMPARISON OF VIA/VILI WITH BIOPSY

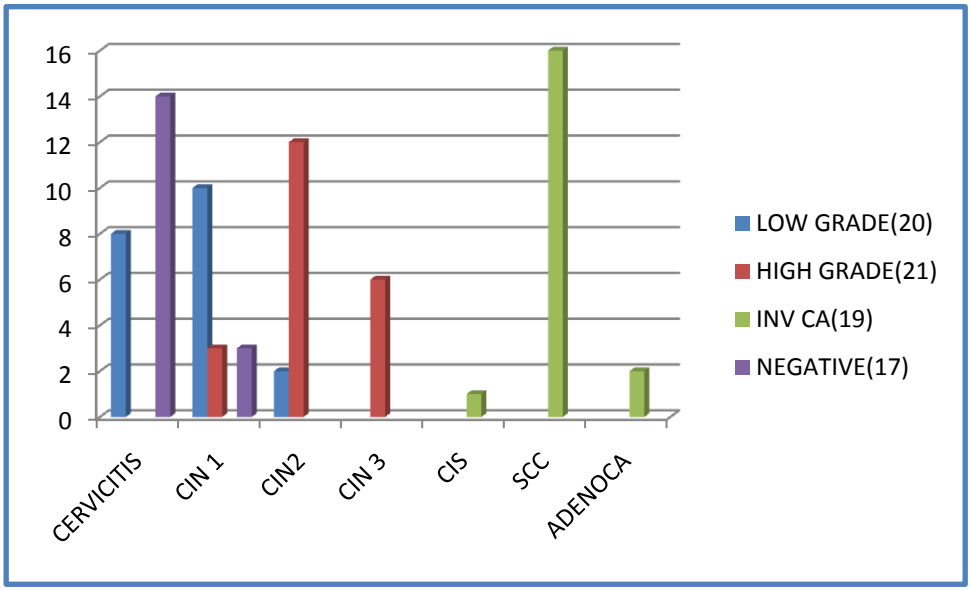


CHART 16

COMPARISON OF CONVENTIONAL PAP WITH BIOPSY

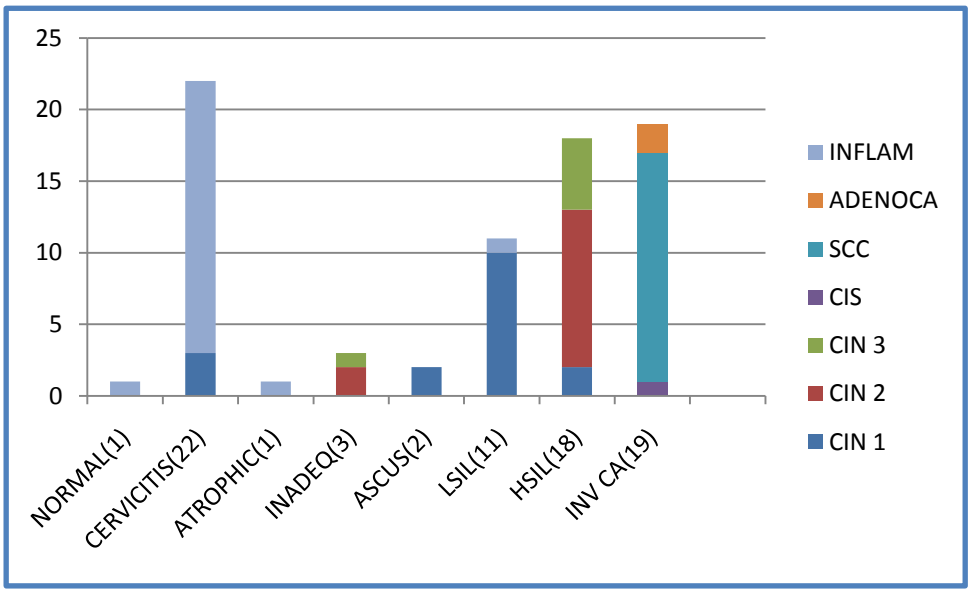


CHART 17

COMPARISON OF LBC WITH BIOPSY

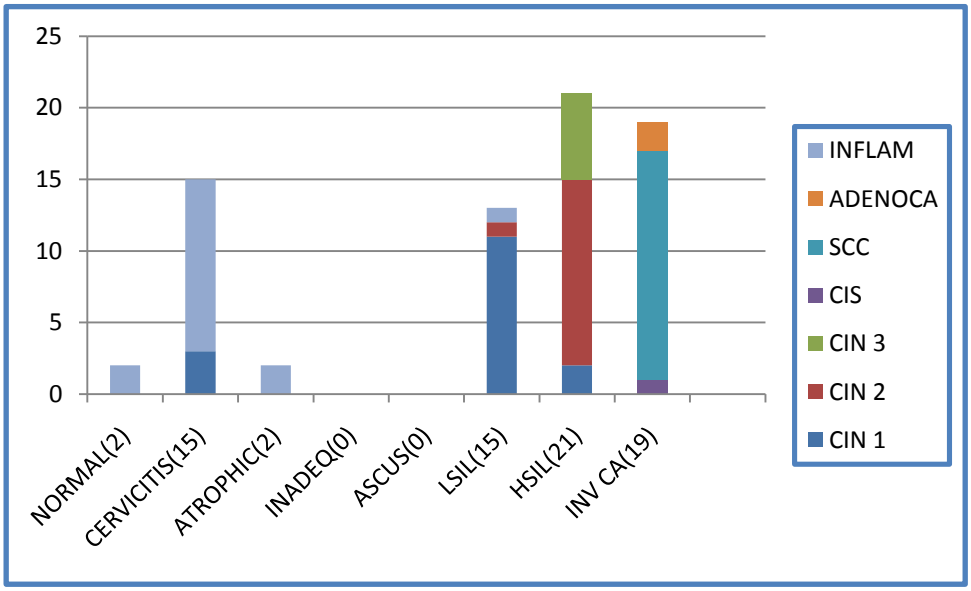


CHART 18

COMPARISON OF CONVENTIONAL PAP WITH LBC

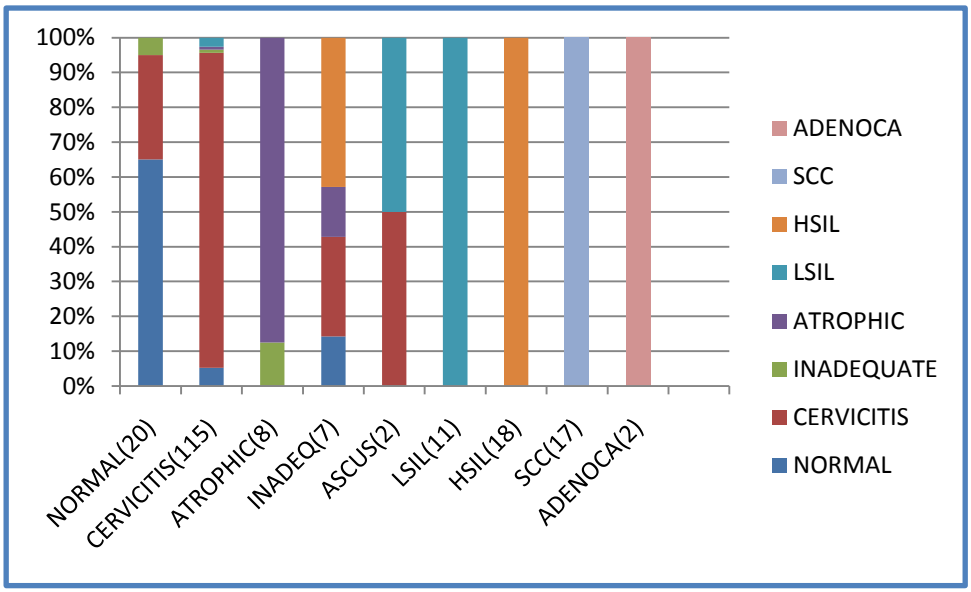


CHART 19

EFFICACY OF VARIOUS SCREENING METHODS

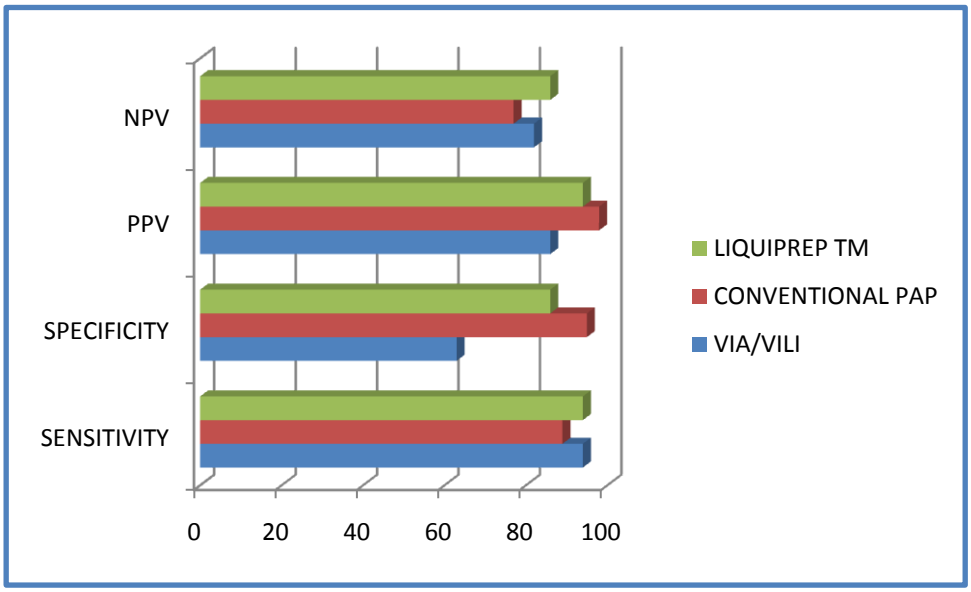
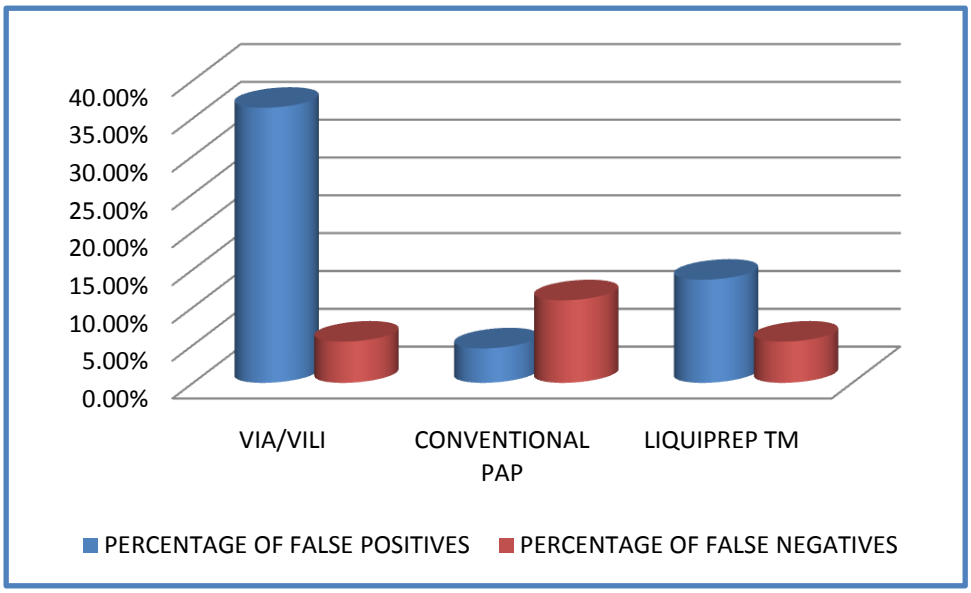


CHART 20

PERCENTAGE OF FALSE POSITIVES AND FALSE NEGATIVES



NORMAL FINDINGS

FIGURE 1: VIA- Normal cervix

FIGURE 2: VILI- Normal cervix

ECTOPY OF CERVIX

FIGURE 3: VIA- Ectopy of cervix

FIGURE 4: VILI- Ectopy of cervix

SATELLITE LESION

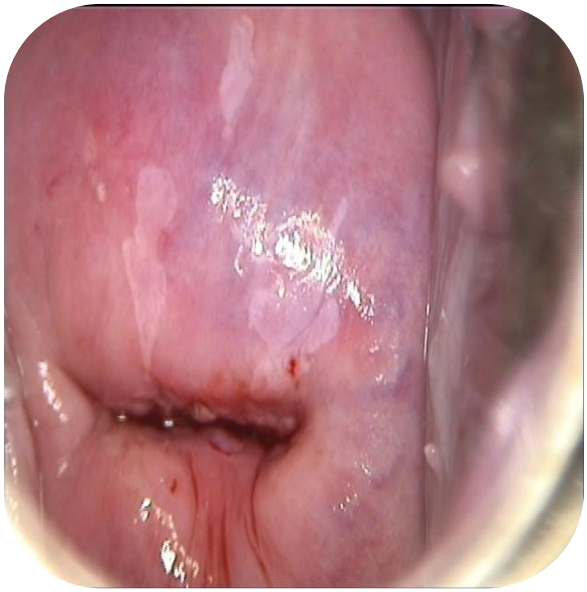


FIGURE 5: VIA- Satellite lesion

FIGURE 6: VILI- Satellite lesion

LEOPARD SKIN APPEARANCE

FIGURE 7: VIA- Leopard skin

FIGURE 8: VIA- Leopard skin

ENDOCERVICAL POLYP

FIGURE 9: VIA- endocervical polyp

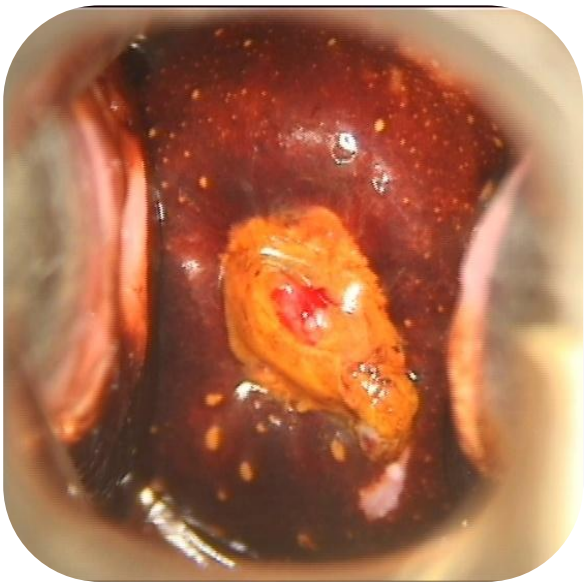


FIGURE 10: VILI- endocervical polyp

LOW GRADE LESION

FIGURE 11: VIA- Low grade lesion

FIGURE 12: VILI- Low grade lesion

HIGH GRADE LESION

FIGURE 13: VIA- High grade lesion

FIGURE 14: VIA- High grade lesion

INVASIVE CARCINOMA

FIGURE 15: VIA- Invasive carcinoma

FIGURE 16: VIA- Invasive carcinoma

NORMAL SMEAR

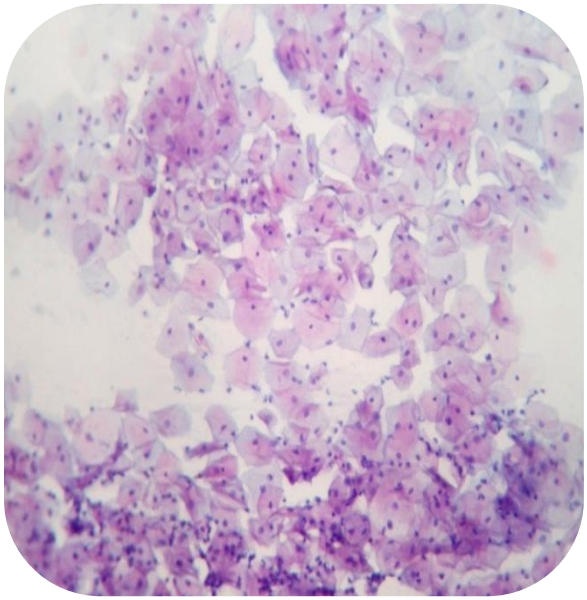


FIGURE 17: Conventional Pap- Normal smear (10X)

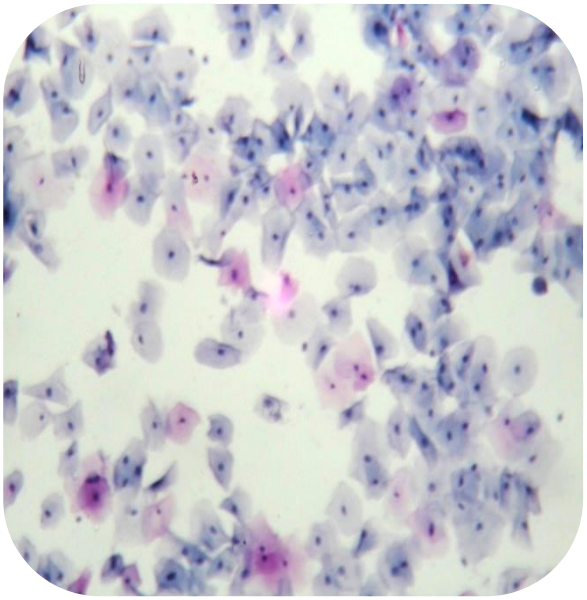


FIGURE 18: LiquiPrep TM- Normal smear (10X)

INFLAMMATORY SMEAR

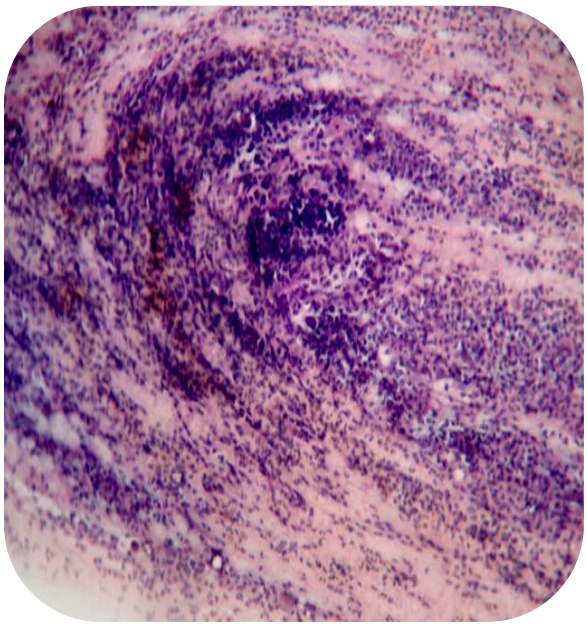


FIGURE 19: Conventional Pap- Inflammatory smear (10X)

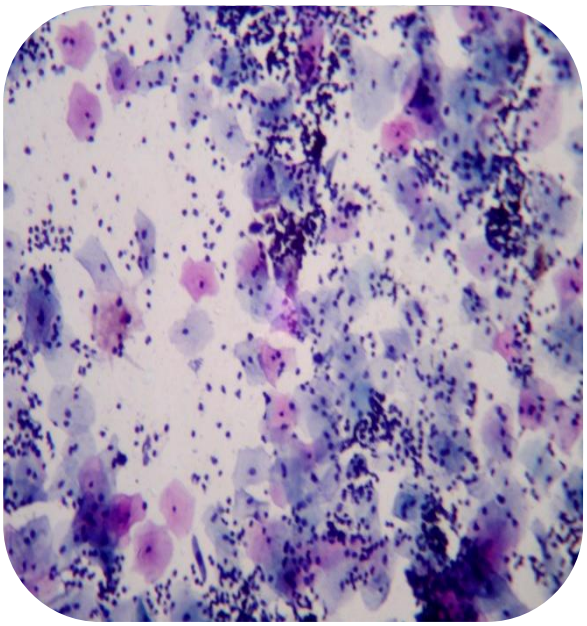


FIGURE 20: LiquiPrep TM- Cervicitis (10X)

INFECTIONS

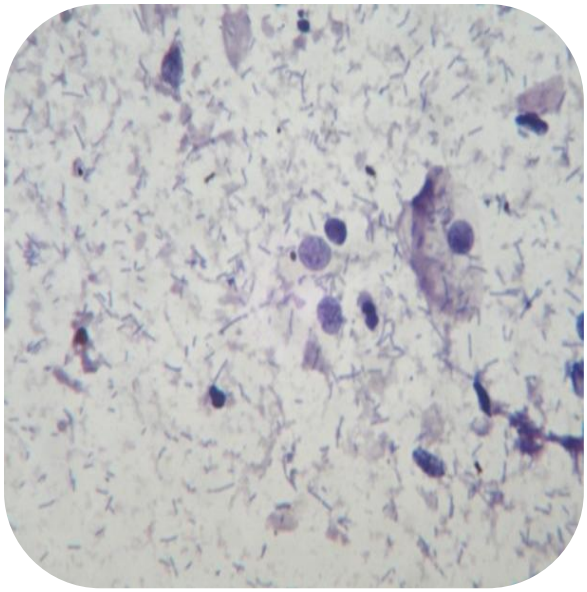


FIGURE 21: Conventional Pap- Trichomonas vaginalis (40X)

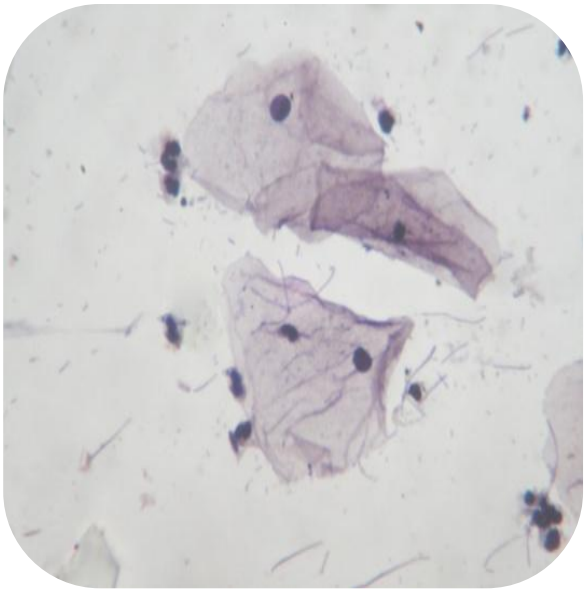


FIGURE 22: Conventional Pap- Candida albicans (40X)

ATROPHIC SMEAR

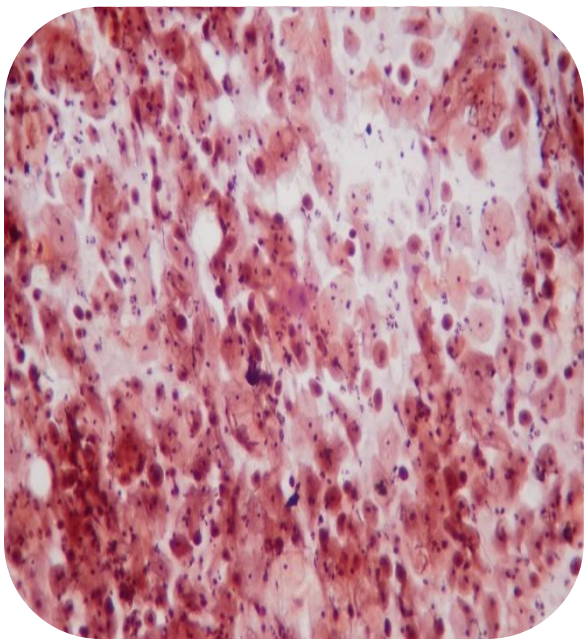


FIGURE 23: Conventional Pap- Atrophic smear (10X)

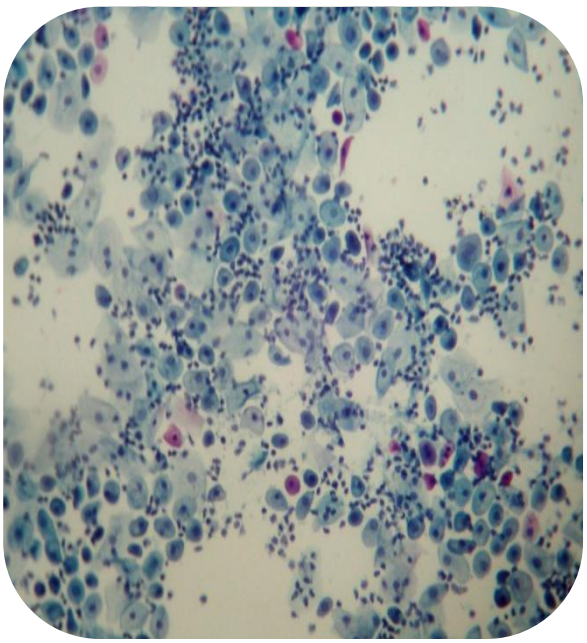


FIGURE 24: LiquiPrep TM- Atrophic smear (10X)

ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE

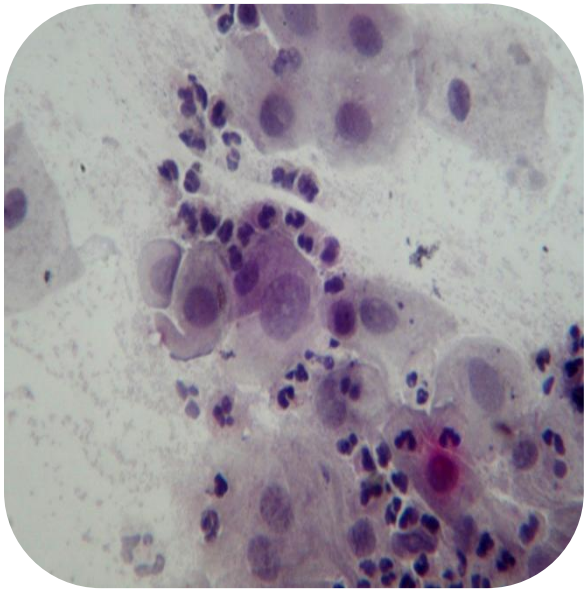


FIGURE 25: Conventional Pap- ASCUS (40X)

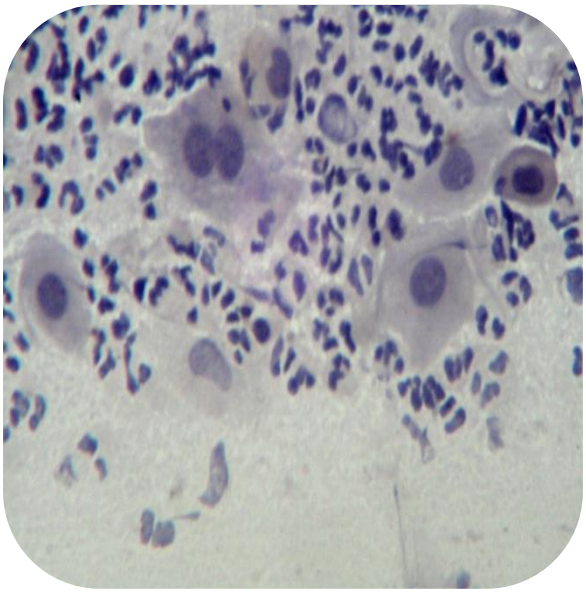


FIGURE 26: Conventional Pap- ASCUS showing binucleate cell (40X)

LOWGRADE SQUAMOUS INTRAEPITHELIAL LESION

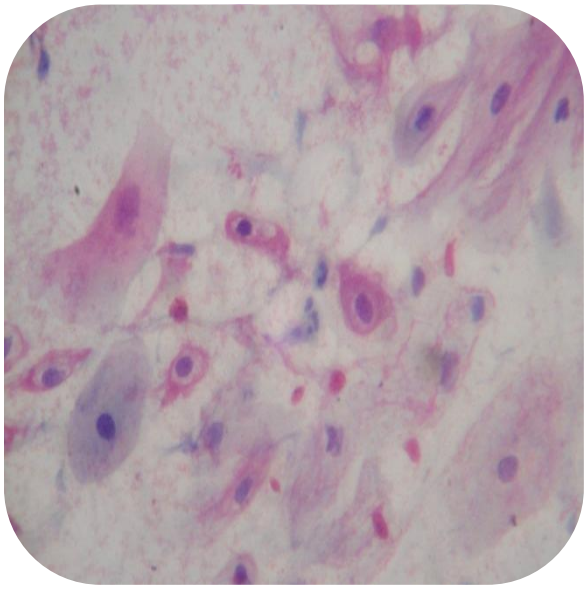


FIGURE 27: Conventional Pap- LSIL (40X)

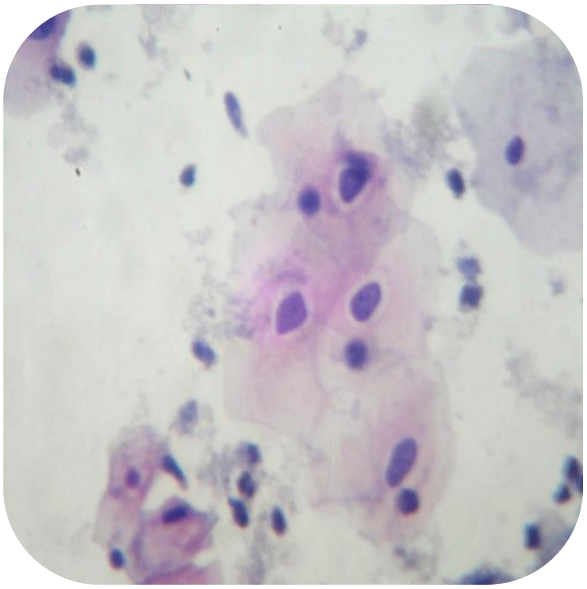


FIGURE 28: LiquiPrep TM- LSIL (40X)

HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION

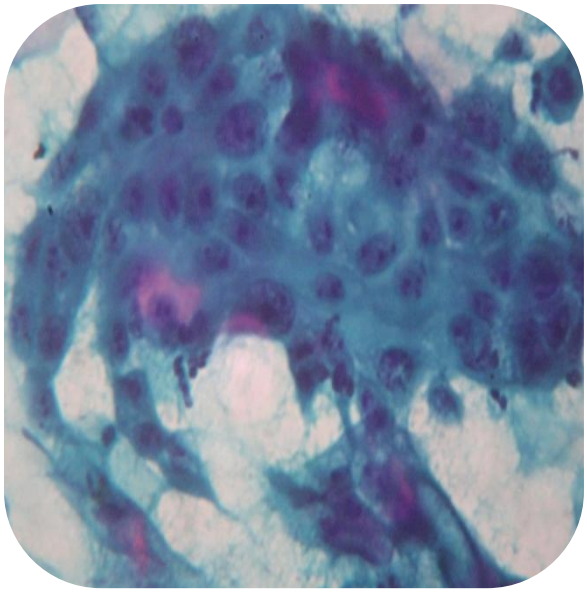


FIGURE 29: Conventional Pap- HSIL (40X)

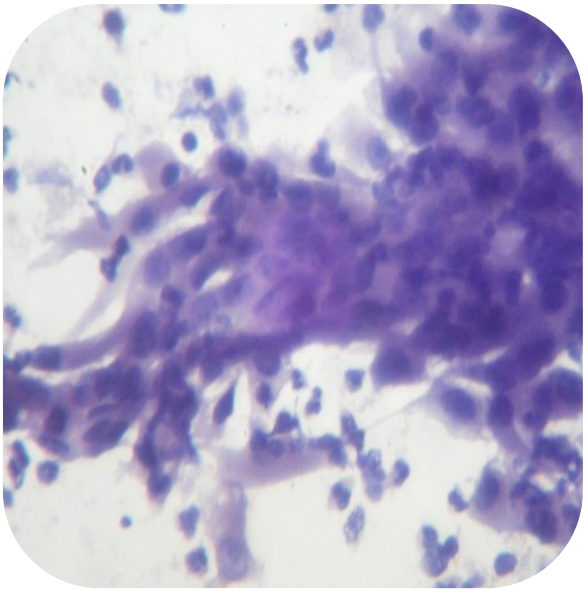


FIGURE 30: LiquiPrep TM- HSIL (40X)

INVASIVE SQUAMOUS CELL CARCINOMA

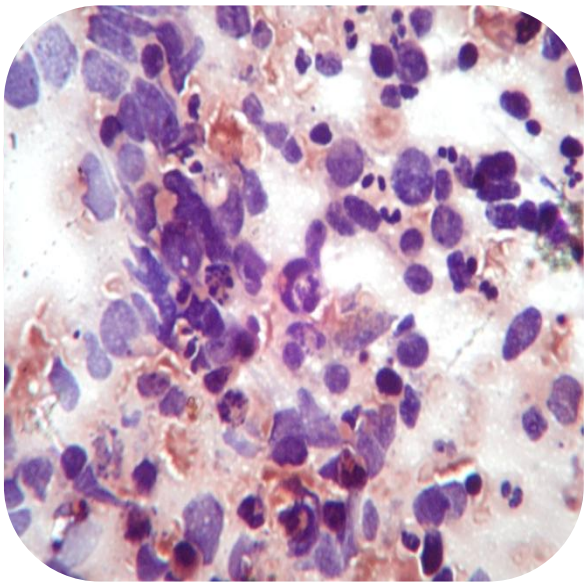


FIGURE 31: Conventional Pap- Invasive squamous cell carcinoma (40X)

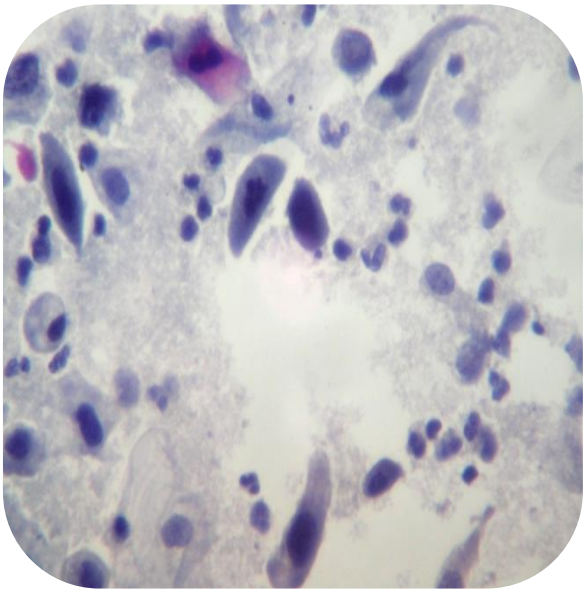


FIGURE 32: LiquiPrep TM- Invasive squamous cell carcinoma (40X)

INVASIVE ADENOCARCINOMA

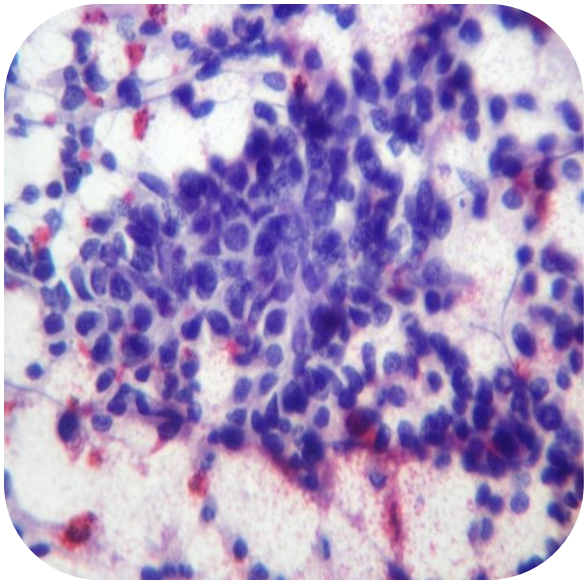


FIGURE 33: Conventional Pap- Invasive Adenocarcinoma cervix (40X)

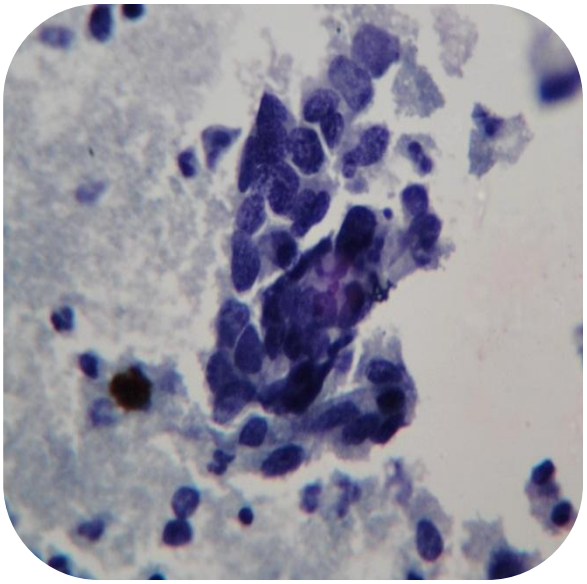


FIGURE 34: LiquiPrep TM- Invasive Adenocarcinoma cervix (40X)

CHRONIC CERVICITIS

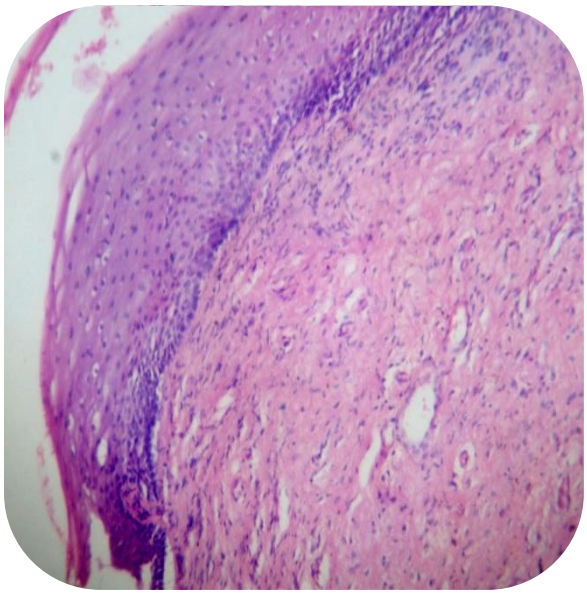


FIGURE 35: HPE- Chronic cervicitis (10X)

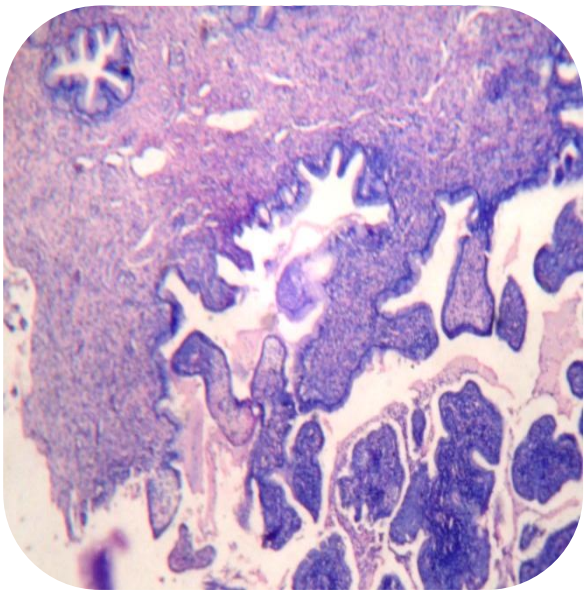


FIGURE 36: HPE- Papillary endocervicitis (10X)

CIN-I

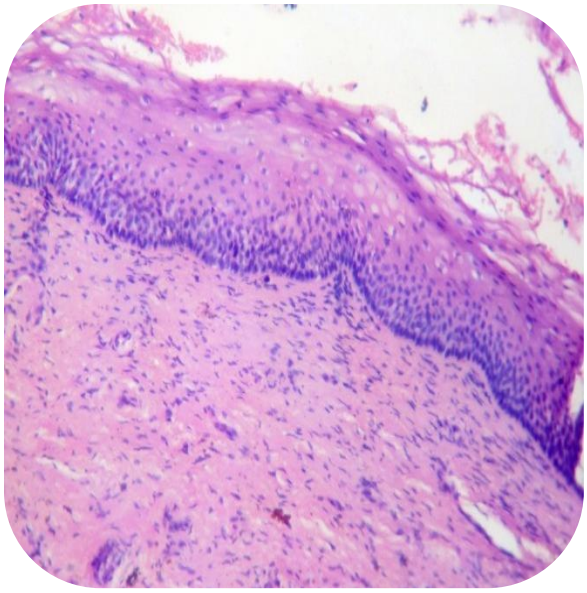


FIGURE 37: HPE- CIN I (10X)

CIN-II

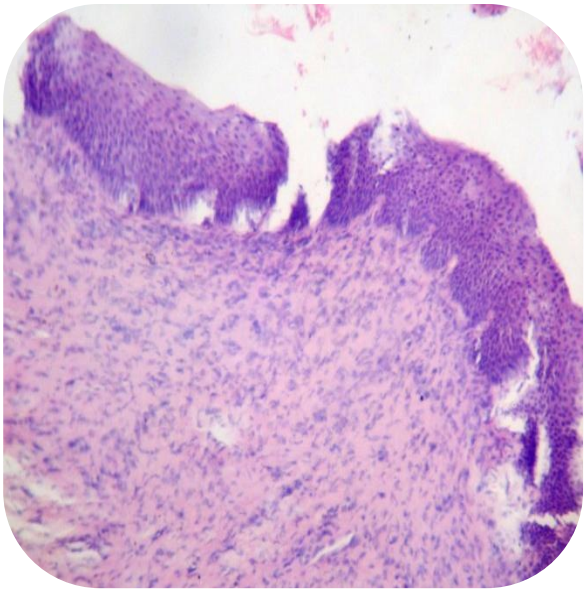


FIGURE 38: HPE- CIN II (10X)

CIN-III

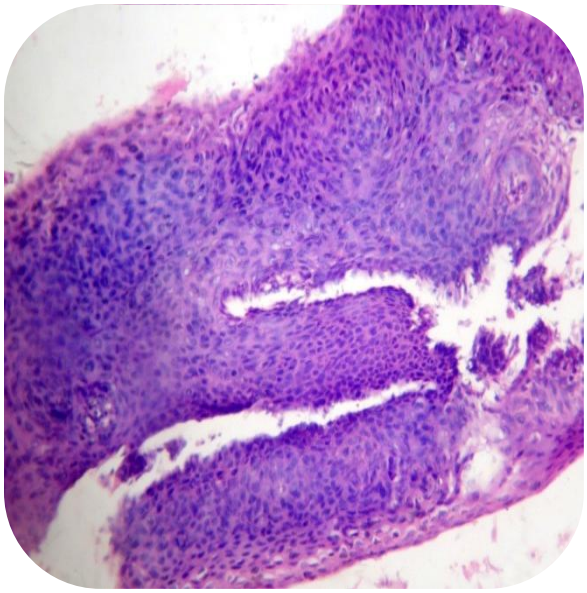


FIGURE 39: HPE- CIN III (10X)

CARCINOMA IN SITU

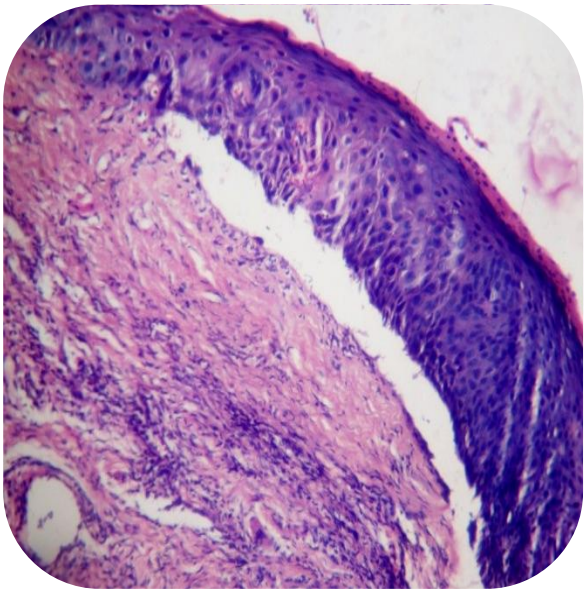


FIGURE 40: HPE- Carcinoma in situ (10X)

SQUAMOUS CELL CARCINOMA

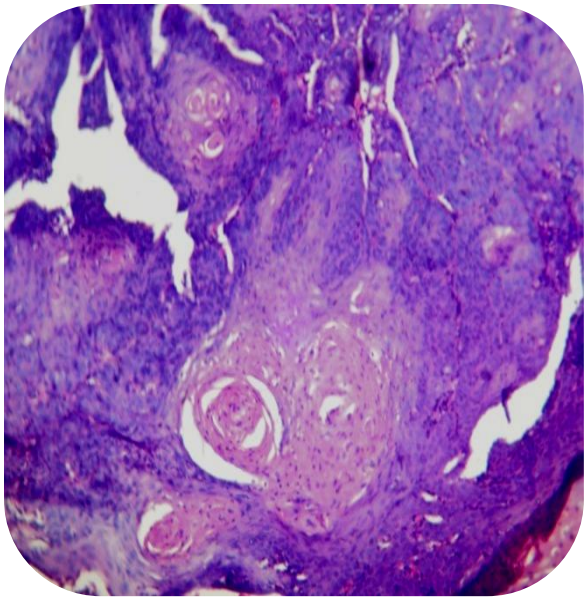


FIGURE 41: HPE- Well differentiated squamous cell carcinoma (10X)

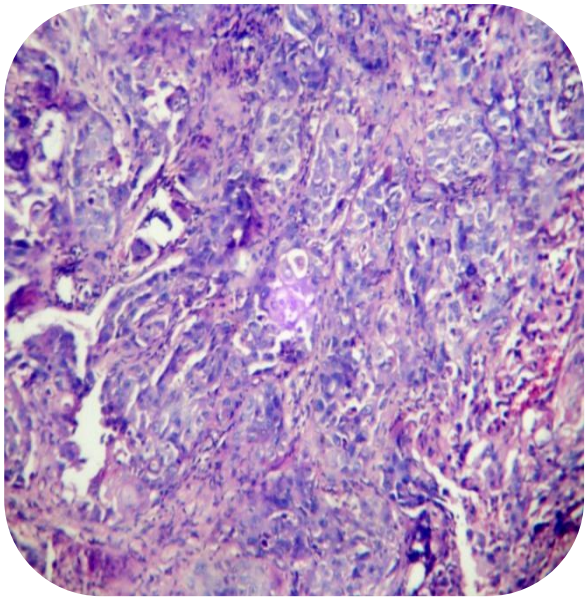


FIGURE 42: HPE- Moderately differentiated squamous cell carcinoma (10X)

POORLY DIFFERENTIATED CARCINOMA

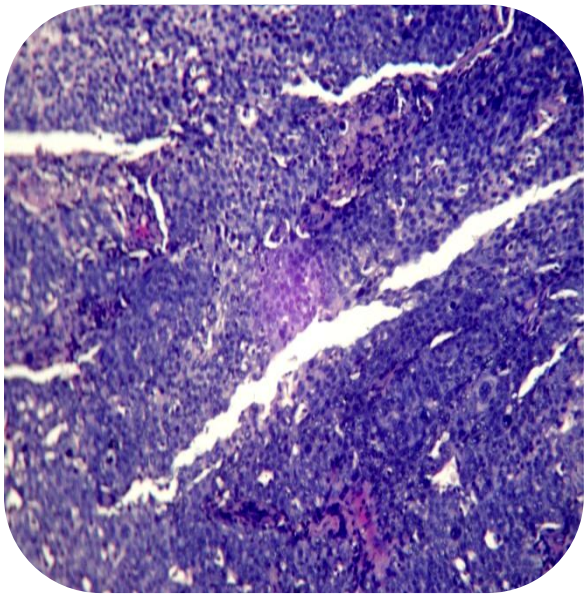


FIGURE 43: HPE-Poorly differentiated squamous cell carcinoma (10X)

ADENOCARCINOMA

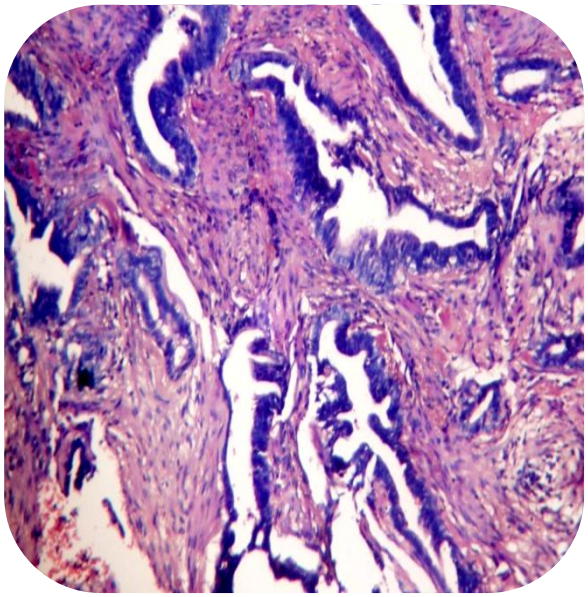


FIGURE 44: HPE- Moderately differentiated adenocarcinoma (10X)

DISCUSSION

DISCUSSION

This prospective comparative study analyses the efficacy of visual inspection methods (VIA/VILI), conventional cytology and liquid based cytology with biopsy as gold standard as an easily interpretable low cost but effective method for cancer cervix.

1. CHARACTERISTICS OF STUDY GROUP

AGE:

- In this study most of the patients were in the age group 31 to 40 years (35%).

- In the cross sectional study done in October 1995 to August 1997women attending 15 primary health center in Zimbabwe[51] to study the efficacy of VIA and cytology in the study group, the age group included was 25 to 55 years and the mean age was 33.25.
- In British Columbia study 1990, the age group of 15 to 18 were 27%, 20 to 34 were 68%, 35 to 59 were 46% and 60 and above were 21% with highest age incidence noted in third and fourth decade[52].
- In a study evaluating the efficacy of VIA with conventional pap smear by Divya Hedge et al[53], 56.6% belonged to the

41-50 year age group and 68.5% belonged to the lower middle age group.

- In a study by SO Albert et al[54] comparing VIA and pap smear the patients were aged between 14 and 45 years with a mean of 28.7 ± 4.2 years.
- A study conducted in AIIMS, New Delhi in 2003[55] to evaluate and compare test performance of visual inspection of cervix by a doctor and paramedical worker, included study group of patients with 64% belonging to 30-39 years.
- In a study comparing the colposcopic and cytologic findings by Maziah AM et al[56], 70% of the patients were between 30-49 years of age.
- Shalini et al[58] showed that 32 year was the mean age of patients with benign pathology in their study. Dysplasia was found to be more common between 20 and 39 years.
- Kushtagi and Fernandes in their study showed the prevalence of dysplasia was higher in women over 30 years[59].

DISTRIBUTION OF SOCIOECONOMIC STATUS IN THE STUDY GROUP:

- In this study most of the patients were in the socioeconomic group 4(37%) and group 5(33.5%).

- In the cross sectional screening test done in Zimbabwe[51] comparing the efficacy of VIA and cytology in the study group, most of the patients were belonging to socioeconomic status 3.
- In a study conducted in Institute of medical sciences, Lahore in 2007[57]showed that all women with CIN belonged to low socio economic status and about 24-80% belonged to very low socio economic status of income between Rs.3000- 5000/month.

DISTRIBUTION OF AGE AT MENARCHE AND AGE AT MARRIAGE IN THE STUDY GROUP:

- In this study most of the patients attained menarche at 13-14 yrs (82%) and 73% of them got married at 15-20 yrs.
- In the cross sectional screening test done in 15 primary health center in Zimbabwe[51], 56% attained menarche at 13 years and most of them got married at 18 years (46%).
- In a study comparing the colposcopic and cytologic findings by Maziah AM et al[56], 44% of the patients were below 19 years of age at first coitus and another 50% from 20-29 years of age.
- A study conducted in AIIMS, New Delhi in 2003[55] showed that the mean age at first sexual intercourse was 19+/- 3.3 years.

DISTRIBUTION OF PARITY AMONG THE STUDY GROUP:

- In this study 46.5% of patients were of parity 2.

- In a study by SO Albert et al[54] comparing VIA and Pap smear , 79.8% patients were multiparous, while 20.2% were grandmultiparous.
- In a study comparing the colposcopic and cytologic findings by Maziah AM et al[56], 92% of the patients were multiparous.

DISTRIBUTION OF SYMPTOMS IN THE STUDY GROUP:

- The most common presenting symptom in the study group (63%) was white discharge per vagina. The common presenting symptom in women with dysplasia was also white discharge per vagina.
- In a study evaluating the efficacy of VIA with conventional pap smear by Divya Hedge et al[53], the major presenting complaint was menstrual irregularities in 40.8% women. 12.9% of women had complaints of white discharge per vagina. White discharge per vagina was the most common presenting complaint among patients in whom precancerous and malignant lesions were detected.

2. VISUAL INSPECTION FINDINGS-VIA AND VILI

- All patients were subjected to colposcopy and visual inspection with acetic acid and Lugol's iodine.
- VIA and VILI positive in 68 cases and in 132 cases the test results were negative. Thus 34% of the screening population showed positive results.

- The above findings correlated with the study conducted by Sankaranarayanan et al[60], in Kolkatta involving 5881 women which showed VIA positive results in 30% .
- Cecchini S et al reported positive VIA in 25.4% in their study[61].

AGEWISE DISTRIBUTION OF VIA/VILI POSITIVE CASES

- In this study, 39.7% of the VIA/VILI positive cases were in the age group of 31-40 years.
- This was similar to the study conducted by Maziah AM[56] et al at Universiti Kebangsaan Malaysia, Kuala Lumpur in which 36% of preclinical cervical cancer were in the age group of 30-39 years.

VIA/VILI RESULTS- SOCIOECONOMIC STATUSWISE

- In this study majority of VIA/VILI positive cases were of socioeconomic class 4 (36.8%) and 5 (30.8%).
- In a study at Institute of Medical sciences Lahore, involving 500 patients, low socioeconomic status was the most common risk factor (44.8%) present in the population screened.

CONVENTIONAL PAP SMEAR CYTOLOGY FINDINGS

- All patients were subjected to conventional Pap smear cytology.
- There were 7 cases (3.5%) which were inadequate, 20 Cases (10%) showed normal findings,8 cases were atrophic (4%), 115 cases

showed features of cervicitis (57.5%), 2 cases showed ASCUS(1%), 11 Cases (5.5%) showed LSIL, 18 cases (9%) showed HSIL. 17 cases (8.5%) showed squamous cell carcinoma and 2 cases (1%) showed adenocarcinoma.

- 3.5% of cases were inadequate for interpretation in this study.
- In a study by M Tunc Canda et al[42] comparing the efficacy of conventional pap smears and Liqui prep TM, 0.8% of conventional smears were inadequate for interpretation.
- Considering ASCUS and above as abnormal, 25% of the screened population showed positive results.
- In a study conducted at Pohang St Mary's Hospital[62] involving 1235 women the percentage of cases which were ASCUS+ was 31%.

LIQUID BASED CYTOLOGY FINDINGS:

- All the 200 patients were subjected to liquid based cytology.
- 3 cases(1.5%) were inadequate, 20 cases(10%) normal, 9 smears(4.5%) were atrophic, 113 cases(56.5%) showed cervicitis, 15 cases(7.5%) were LSIL, 21 cases(10.5%) showed HSIL. 17 cases(8.5%) were squamous cell carcinomas and 2 cases(1%) were adenocarcinomas.
- In this study the rate of inadequate smears was 1.5%.

- In the study by M Tunc Canda et al[42], Liquiprep smears were inadequate only in 0.1%.
- There were no cases of ASCUS in LBC.
- Cases which were LSIL and above (27.5%) were considered abnormal.
- University of Zimbabwe _ JHPIEGO Cervical Cancer Project[51] found that 14.6% of the women in their study had an abnormal Pap smear.

BIOPSY FINDINGS:

- Biopsy was done in all cases which showed VIA/VILI positivity and in cases which were ASCUS+ on Pap cytology.
- Biopsy was not done in 8 low grade lesions on colposcopy as they were negative for squamous intraepithelial lesion on both conventional and liquid based cytology.
- Biopsy was also done in 12 cases who showed no abnormal results in VIA/VILI and pap smear as control.
- 22 cases (28.5%) showed cervicitis on biopsy, 16 cases (20.8%) showed CIN 1, 14 cases (18.2%) showed CIN 2, 6 cases (7.8%) were CIN 3, 1 case (1.3%) showed carcinoma in situ with focal microinvasion. 16 cases (20.8%) revealed invasive squamous cell carcinoma and 2 cases (2.6%) were adenocarcinoma.

- In the study conducted by Longatto filho et al[63] in 2005 involving 10,000 women, the results of biospy were 2500 normal cases (54%), 1860 inflammatory (42%), dysplasia in 80 cases (4%), mild dysplasia (2%), moderate dysplasia (2%).

AGEWISE DISTRIBUTION OF BIOPSY RESULT:

- In this study the most common age group of CIN is 31-40 years whereas invasive carcinoma is common above the age group of 50 years.
- Kushtagi and Fernandes in their study showed the prevalence of dysplasia was higher in women over 30 years[59].
- Shalini et al[58] showed 25% of well differentiated and 35% of moderately differentiated carcinomas in the age group 40-49, 50% of well differentiated and 57% of moderately differentiated carcinoma was in age group > 50. The mean age of patient with cancer cervix was 41.

COMPARISION OF VIA/VILI RESULTS WITH BIOPSY:

- Among the 20 low grade lesions, 8 were cervicitis, 10 were CIN 1 and 2 cases were diagnosed as CIN 3 on biopsy.
- 21 high grade lesions were reported CIN 1: 3 cases, CIN 2: 12 cases and CIN 3: 6 cases.
- Out of 19 cases of invasive carcinomas, 1 case was carcinoma in situ, 16 cases were reported as SCC and 2 cases were reported as adenocarcinoma on biopsy.

- In our study the sensitivity of VIA/VILI was 94.55%, specificity was 63.64%, Positive predictive value was 86.67% and negative predictive value was 82.35%.
- The sensitivity, specificity, PPV and NPV of various studies are tabulated below:

STUDY	**SENSITIVITY %**	**SPECIFICITY %**	**PPV %**	**NPV %**
Present study	94.55	63.64	86.67	82.35
Divya Hedge et al[53] (2011)	70.8	95	96.5	62.9
Shankaranarayanan et al[60] (2001)	90	92	17	97
Zimbabwe/ JHPIEGO[51] Phase I	NA	NA	25.9	73.3
Phase II	76.7	64.1	18.6	73.3
Goel et al[64] (2005)	96.7	36.4	58	99.7
Singh KN et al[65] (2010)	93.1	86.8	22.1	99
Bhatla N et al[66] (2007)	100	53.3	15.7	100
Rana T et al	93	90	62.5	98.8

- False positive cases were 8 cases of low grade lesions on colposcopy reported as cervicitis on biopsy.
- False negative cases were 2 cases of ectopy and one case of satellite lesion on colposcopy which were CIN 1 on biopsy .

COMPARISION OF CONVENTIONAL PAP SMEAR WITH BIOPSY:

- 1 normal smear was reported as cervicitis on biopsy.
- 22 cases of cervicitis on Pap smear were given as cervicitis- 19 and CIN 1- 3 on biopsy.
- 1 atrophic smear was reported as cervicitis. 3 inadequate smears were reported as CIN 2- 2 and CIN 3- 1.
- 2 cases of ASCUS were CIN 1 on biopsy. 11 cases of LSIL were given as CIN 1-10 and cervicitis- 1.
- 18 cases of HSIL turned out to be CIN 1- 2, CIN 2-11, CIN 3-5.
- 19 cases of invasive carcinoma were reported carcinoma in situ with focal microinvasion- 1, SCC- 16 and adenocarcinoma- 2 on biopsy.
- The sensitivity, specificity, PPV and NPV of various studies are tabulated below:

STUDY	SENSITIVITY %	SPECIFICITY %	PPV %	NPV %
Present study	89.09	95.45	98	77.78
Divya Hedge et al[53] (2011)	83	98	97.9	80
Shankaranarayanan et al[60] (2001)	86	91	22	99
Jang JH et al[62] (1992-2001)	82.7	95.5		
Goel et al[64] (2005)	50	97	97.5	96.09
Singh KN et al[65] (2010)	70.02	97.2	51.2	97
Hussein T et al[66]	92	76	57	96
Mahmood Khaniki et al[67]	66	86	33	96
Hua Chen et al[68]	43.08	97.2	70	91.85
Nadereh Behtash[69]	58	88	33	96
Rana T et al[70]	83.3	97	83	97

- False positive was 1 case of LSIL on conventional pap smear which was reported as chronic cervicitis on biopsy.
- False negative cases were 6 cases: 2 cases of CIN 1 on biopsy were reported as cervicitis on pap smear.1 case of CIN 1 was reported as

inflammatory smear on pap. 2 cases of CIN 2 and 1 case of CIN 3 were inadequate for interpretation on conventional pap smear.

COMPARISON OF LBC RESULTS WITH BIOPSY:

- 2 normal smears were reported as cervicitis on biopsy.
- 15 cases of cervicitis on LBC smear were given as cervicitis- 12 and CIN 1- 3 on biopsy.
- 2 atrophic smears were reported as cervicitis.
- 15 cases of LSIL were given as CIN 1-11, CIN 2- 1 and cervicitis- 3.
- 21 cases of HSIL turned out to be CIN 1- 2, CIN 2-13, CIN 3-6.
- 19 cases of invasive carcinoma were reported as carcinoma in situ with focal microinvasion- 1, SCC- 16 and adenocarcinoma- 2 on biopsy.

STUDY	**SENITIVITY %**	**SPECIFICITY %**	**PPV %**	**NPV %**
Present study	94.55	86.36	94.55	86.36
Hussein T et al[66]	83	82	62	93
Mahmood Khaniki et al[67] (Liquiprep TM)	83	98	83	96
Longatto Filho et al[68] (ThinPrep)	33.3	100	100	88.8

Hua Chen et al[68] (ThinPrep)	80	63.16	16	97.3
Nadereh Behtash et al[69] (Liquiprep TM)	86	98.5	86	98.5
Lee HS et al[71] (Thin Prep)	79	98		
Lee KC et al[72] (Thin Prep)	85.1	98.3		
Lee KC et al[73] (Surepath TM)	91.7	75.9		
Lim YK et al[74] (MonoPrep)	94.9	92.3		

There were 3 cases of false positive- reported as LSIL on LBC smear and cervicitis on biopsy. False negative cases were 3 cases which were CIN 1 on biopsy but reported as cervicitis on LBC.

COMPARISION OF VARIOUS SCREENING PROCEDURES:

- The sensitivity was highest for both VIA/VILI and Liqui Prep TM and was similar (94.55%). However the specificity was highest for conventional pap smear (95.45%).
- Positive predictive value was highest for conventional pap smear (98%) followed by LiquiPrep TM (94.55%).
- Negative predictive value was highest for LiquiPrep TM (86.36%) followed by VIA/VILI (82.35%).
- The percentage of false positives was highest with VIA/VILI (36.36%) and lowest with conventional pap smear (4.55%).
- The percentage of false negatives was highest with conventional pap smear (10.91%) and both LiquiPrepTM and VIA/VILI showed a lower percentage of false negatives (5.45%).

COMPARISON OF CONVENTIONAL PAP AND LIQUIPREP TM:

- Conventional pap smears were inadequate in 3.5% whereas LiquiPrepTM smears were inadequate in 1.5%.
- Hussein T et al[66] showed that the rate of inadequacy was 4.3% for conventional pap while it was 0.68% for LBC.
- There were 115 cervicitis smears (57.5%) on conventional pap smear but only 113 cervicitis smears on LBC (56.5%).

- In a study by Nadereh Behtash et al[69] conducted at Iran on 506 patients, 26% of conventional pap smears were inflammatory whereas only 19% of LBC smears were inadequate.
- In this study, the percentage of concordance of conventional pap smear with biopsy was 100% for ASCUS, 90.1% for LSIL, 88.89% for HSIL and 100% for invasive carcinoma.
- In a study by Deshou et al[75] at Jiangxi Province Women and Child Health Care Hospital, the concordance rate of conventional smear was 80% for ASCUS, 78.9% for LSIL, 76.1% for HSIL and 89.5% for SCC.
- Joonseok Park et al[76] in a study comparing the efficacy of conventional pap smear and Liquiprep TM, showed that the concordance rate of conventional pap smear was 89.2% for LSIL and 93.6% for HSIL.
- In this study, the percentage of concordance of LiquiprepTM Pap smear with biopsy was 80% for LSIL, 90.47% for HSIL and 100% for invasive carcinoma. The lower concordance rate for LSIL could be due to error in the sampling area for biopsy.
- In a study by Deshou et al[75], the concordance rate of conventional smear was 93.9% for ASCUS, 95.4% for LSIL, 90.2% for HSIL and 94.7% for SCC.

- Joonseok Park et al[76] in their study showed that the concordance rate of conventional pap smear was 93.5% for LSIL and 95.5% for HSIL.
- In this study the detection rate of ASCUS is 1%, for LSIL is 5.5% and for HSIL is 9% in conventional pap, whereas the detection rate of LSIL is 7.5% and of HSIL is 10.5%.
- Out of the 2 cases of ASCUS on conventional pap, one was reported as cervicitis and another as LSIL on LBC.
- In the study by Hussein T et al[66] , the detection rates of HSIL were similar for both conventional pap and LBC but the detection rate of LSIL was greater for LBC (ThinPrepTM) compared to conventional pap.

SUMMARY

SUMMARY

- This is the study conducted at Kasturba Gandhi Hospital for women and children to study the efficacy of VIA/VILI, conventional pap and LBC with biopsy as gold standard in low resource country like India.
- VIA/VILI, conventional pap smear and liquid based cytology were done in all 200 patients.
- Those cases showing VIA/VILI Positive (or) cytology positive were subjected to cervical biopsy except for 12 cases which were negative on VIA/VILI and cytology for which biopsy was done (as control).
- Majority of women enrolled in the study belonged to the age group of 31-40 years, were of socioeconomic grade 4 or 5, attained menarche at 13-14 years of age, had their marriages around 15-20 years, were of parity 2.
- The most common presenting symptom in the study group was white discharge per vagina (63%).
- VIA/VILI was positive in 68 cases (34%) and 132 cases (68%) showed negative results.
- 39.7% of the patients who were VIA/VILI positive belonged to 31-40 years age group.
- Majority of the patients who were VIA/VILI positive were of socioeconomic grade 4 or grade 5.

- Pap smear report was inadequate in 7 patients (3.5%), normal in 20 patients (10%), atrophic smear in 8 patients (4%), Cervicitis in 115 patients (57.5%), ASCUS in 2 patients (1%), LSIL in 11 patients (5.5%), HSIL in 18% (9%), SCC in 17 patients (8.5%) and adenocarcinoma in 2 patients (1%).
- LBC report was inadequate in 3 patients (1.5%), normal in 20 patients (10%), atrophic smear in 9 patients (4.5%), Cervicitis in 113 patients (56.5%), LSIL in 15 patients (7.5%), HSIL in 21% (10.5%), SCC in 17 patients (8.5%) and adenocarcinoma in 2 patients (1%).
- Biopsy was reported as cervicitis in 22 cases (28.5), CIN 1 in 16 cases (20.8%), CIN 2 in 14 cases (18.2%), CIN 3 in 6 cases (7.8%), carcinoma in situ with focal microinvasion in 1 case (1.3%), SCC in 16 cases (20.8%) and adenocarcinoma in 2 cases (2.6%).
- The most common age group of CIN is 31-40 years whereas invasive carcinoma is common above the age group of 50 years.
- Out of 20 low grade lesions, 12 showed dysplasia on biopsy. All the 21 high grade lesions showed dysplasia on biopsy.
- 3 negative cases, 3 inadequate cases and both the cases of ASCUS, and all cases of HSIL showed dysplasia on biopsy. Among the cases of LSIL, 1 case failed to show dysplastic changes on biopsy. This may be due to the error in the area sampled for biopsy.

- 3 cases of cervicitis and all cases of HSIL showed dysplasia on biopsy. Among the 15 LSIL cases, 12 were dysplastic on biopsy.
- 2 cases which were diagnosed as ASCUS on conventional pap were reported as LSIL and cervicitis on LBC.
- The percentage of concordance of conventional pap smear with biopsy was 100% for ASCUS, 90.1% for LSIL, 88.89% for HSIL and 100% for invasive carcinoma.
- The percentage of concordance of Liquiprep TM pap smear with biopsy was 80% for LSIL, 90.47% for HSIL and 100% for invasive carcinoma.
- Both VIA/VILI and LBC had similar sensitivity rates in the screening of cancer cervix compared to conventional Pap smear. However the specificity and PPV were highest for the conventional pap smear followed by LBC. Liquiprep TM had the highest negative predictive value.

CONCLUSION

CONCLUSION

- This correlative study of VIA/VILI, conventional pap smear and LiquiPrepTM smear with histopathological examination of cervix revealed that VIA/VILI and LiquiPrepTM had similar sensitivity of 94.55% which was higher than that of conventional pap smear.
- Specificity was significantly higher with conventional pap smear (95.45%). LiquiPrepTM had a lower specificity than conventional pap, however it was higher than that of VIA/VILI.
- Conventional pap and LiquiPrepTM had higher positive predictive values whereas LiquiPrep TM had the highest negative predictive value followed by VIA/VILI.
- VIA/VILI showed the highest percentage of false positives while the false negatives were highest with conventional Pap smear.
- In conclusion, VIA/VILI can be used as an initial screening test for cervical cancer in a low resource country like India.
- The false negative and false positive cases in this study can be minimized by proper screening and interpretation and further follow up by cytological smears.
- Conventional pap because of its high specificity can be used for followup of low grade lesions on colposcopy.
- LiquiPrepTM has a higher sensitivity equal to that of VIA/VILI and a comparatively higher specificity compared to VIA/VILI and therefore can be used for screening in conditions when there are no financial constrains.

ANNEXURES

ANNEXURE- I

PROFORMA

NAME

AGE

OP/IP NO

OCCUPATION

SOCIOECONOMIC STATUS

ADDRESS

AGE AT MENARCHE

AGE AT MARRIAGE

PARITY

LCB

H/O SEXUALLY TRANSMITTED DISEASE

PAST H/O HT/DM/ASTHMA/EPILEPSY/ TB

PAST H/O SURGERY (ABDOMINAL)

CONTRACEPTIVE HISTORY

PERMANENT / TEMPORARY

-STERILISATION:

Puerperal Sterilisation

Trans abdominal tubectomy – {Interval or

Lap sterilization concurrent with MTP }

Caesarian section with sterilization

GENERAL EXAMINATION

HEIGHT

WEIGHT

BUILD / NOURISHMENT

ANEMIA JAUNDICE

THYROID BREAST

VITALS SIGNS: PULSE RATE, BLOOD PRESSURE,

RESPIRATORY RATE, TEMP

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM

RESPIRATORY STYSTEM

ABDOMINAL EXAMINATION

SPECULUM EXAMINATION

VISUAL INSPECTION WITH ACETIC ACID

VISUAL INSPECTION WITH LUGOL'S IODINE

CONVENTIONAL PAPSMEAR CYTOLOGY

LIQUIPREPTM SMEAR CYTOLOGY

BIOPSY REPORT

FOLLOW UP ACTION

ANNEXURE- II

THE BETHESDA SYSTEM (TBS) 2001 CLASSIFICATION

ADEQUACY OF THE SPECIMEN
Satisfactory for evaluation Unsatisfactory for evaluation
GENERAL CATEGORISATION
Negative for intraepithelial lesion or malignancy
Epithelial cell abnormalities
Squamous Cell Atypical squamous cells (ASC) Atypical squamous cells – undetermined significance (ASCUS) Atypical squamous cells – cannot exclude HSIL (ASC-H) Low-grade squamous intraepithelial lesion (LSIL) encompassing human papillomavirus and mild dysplasia/CIN 1 High-grade squamous intraepithelial lesion (HSIL) encompassing moderate and severe dysplasia, CIS/ CIN 2 and CIN 3 Squamous cell carcinoma
Glandular cell Atypical glandular cells Atypical glandular cells (unqualified)

Atypical endocervical cells (unqualified) Atypical endometrial cells (unqualified) Atypical glandular cells, favor neoplastic Atypical endocervical cells, favor neoplastic Adenocarcinoma in situ (AIS) Endocervical adenocarcinoma Endometrial adenocarcinoma Adenocarcinoma, nonspecific
Other Hormonal evaluation (applies to vaginal smears only) Hormonal pattern compatible with age and history Hormonal pattern incompatible with age and history (specify) Hormonal evaluation not possible because of. . .(specify)

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MASTER CHART

MASTER CHART

S.NO	PAP.NO	AGE	SE STATUS	AGE AT MENARCHE	AGE AT MARRIAGE	PARITY	SYMP-TOMS	PS	VIA	VILI	CONV PAP	LBC	BIOPSY
1	1/11	43	3	14	20	2	WHITE DIS	+	_	_	OESTROG	OESTROG	
2	2/11	40	4	13	36	0	WHITE DIS	_	_	_	OESTROG	OESTROG	
3	3/11	31	3	13	17	4	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
4	4/11	28	4	14	21	2	AUB	+	_	_	INFLAM	OESTROG	
5	5/11	47	4	14	16	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
6	6/11	64	2	15	20	5	WHITE DIS	_	_	_	ATROPH	ATROPH	CERVICITIS
7	7/11	20	3	13	17	2	AUB	+	_	_	INFLAM	INFLAM	
8	8/11	32	4	12	20	3	AUB	_	_	_	CERVICITIS	CERVICITIS	
9	9/11	35	4	13	24	3	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 2
10	10/11	30	3	14	22	1	WHITE DIS	_	_	_	CERVICITIS	CERVICITIS	
11	11/11	30	5	13	21	2	WHITE DIS	_	_	_	INFLAM	CERVICITIS	
12	12/11	30	3	12	19	2	WHITE DIS	_	_	_	INFLAM	INFLAM	
13	13/11	47	4	13	20	3	AUB	+	_	_	INADEQ	CERVICITIS	
14	14/11	28	5	13	18	2	WHITE DIS	+	_	_	OESTROG	OESTROG	
15	15/11	29	4	13	19	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
16	16/11	35	5	12	33	1	WHITE DIS	+	_	_	CERVICITIS	OESTROG	CERVICITIS
17	17/11	50	2	14	15	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
18	18/11	37	4	14	15	3	PRURITIS	+	_	_	CERVICITIS	CERVICITIS	
19	19/11	47	4	13	17	2	WHITE DIS	+	_	_	INFLAM	CERVICITIS	
20	20/11	42	3	13	20	3	WHITE DIS	+	LG	LG	INFLAM	INFLAM	CERVICITIS
21	21/11	34	4	15	19	4	WHITE DIS	+	_	_	INFLAM	CERVICITIS	

22	22/11	51	4	12	16	4	AUB	+	INV CA	INV CA	ADENO CA	ADENO CA	MD ADENO CA
23	23/11	35	5	14	22	2	WHITE DIS	+	LG	LG	INFLAM	CERVICITIS	CERVICITIS
24	24/11	39	5	12	27	2	WHITE DIS	_	_	_	INFLAM	INFLAM	
25	25/11	38	4	13	18	0	WHITE DIS	_	_	_	CERVICITIS	CERVICITIS	
26	26/11	42	3	16	24	3	WHITE DIS	+	_	_	NOR	NOR	
27	27/11	48	4	13	16	2	AUB	_	_	_	ATROPH	ATROPH	
28	28/11	50	2	14	25	2	WHITE DIS	+	LG	LG	LSIL	LSIL	CERVICITIS
29	29/11	40	4	14	18	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
30	30/11	39	3	13	19	2	WHITE DIS	+	LG	LG	CERVICITIS	CERVICITIS	
31	31/11	27	5	13	18	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
32	32/11	60	4	13	25	1	WHITE DIS	_	_	_	INFLAM	INFLAM	
33	33/11	33	5	15	16	3	WHITE DIS	+	LG	LG	HSIL	HSIL	CIN 2
34	34/11	50	4	13	15	5	AUB	_	HG	HG	HSIL	HSIL	LG CIN
35	35/11	41	3	14	19	3	WHITE DIS	+	_	_	INFLAM	INFLAM	
36	36/11	30	4	14	16	4	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 1-2
37	37/11	26	4	14	19	2	WHITE DIS	+	_	_	CERVICITIS	INFLAM	CERVICITIS
38	38/11	35	3	13	20	2	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 2
39	39/11	35	4	14	24	3	AUB	+	HG	HG	HSIL	HSIL	CIN 2
40	40/11	47	2	15	17	4	AUB	+	INV CA	INV CA	SCC	SCC	MD SCC
41	41/11	53	4	13	18	0	WHITE DIS	_	INV CA	INV CA	SCC	SCC	PD SCC
42	42/11	24	4	12	17	3	WHITE DIS	+	LG	LG	CERVICITIS	CERVICITIS	
43	43/11	29	3	14	19	2	WHITE DIS	+	_	_	OESTROG	CERVICITIS	
44	44/11	40	3	15	25	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
45	45/11	36	4	13	22	2	WHITE DIS	+	_	_	INFLAM	INFLAM	
46	46/11	65	3	12	23	3	AUB	_	POST MENO	POST MENO	ATROPH	ATROPH	

47	47/11	32	4	14	23	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
48	48/11	41	4	13	24	2	WHITE DIS	_	_	_	CERVICITIS	CERVICITIS	
49	49/11	27	4	13	17	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
50	50/11	50	5	13	20	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
51	51/11	40	5	13	17	2	PRURITIS	+	_	_	INFLAM	CERVICITIS	
52	52/11	41	3	11	16	3	WHITE DIS	+	_	_	INFLAM	CERVICITIS	
53	53/11	48	4	14	18	2	PAIN ABD	_	_	_	INFLAM	CERVICITIS	
54	54/11	50	5	13	17	3	WHITE DIS	_	_	_	INFLAM	INFLAM	
55	55/11	30	4	13	16	2	WHITE DIS	+	_	_	INFLAM	INFLAM	
56	56/11	47	5	14	17	4	AUB	+	POST MENO	POST MENO	ATROPH	INADEQ	
57	57/11	55	4	13	20	3	AUB	+	INV CA	INV CA	SCC	SCC	PD SCC
58	58/11	25	2	12	19	2	WHITE DIS	+	NOR	NOR	CERVICITIS	CERVICITIS	
59	59/11	40	4	14	21	2	WHITE DIS	+	_	_	INFLAM	CERVICITIS	CERVICITIS
60	60/11	35	4	14	17	2	WHITE DIS	+	LG	LG	CERVICITIS	CERVICITIS	CERVICITIS
61	61/11	42	3	13	16	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
62	62/11	45	5	11	18	2	PAIN ABD	_	_	_	NOR	CERVICITIS	
63	63/11	40	3	13	18	3	WHITE DIS	+	LG	LG	NOR	CERVICITIS	CERVICITIS
64	64/11	40	4	13	15	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
65	65/11	24	2	13	22	1	WHITE DIS	_	_	_	INFLAM	CERVICITIS	
66	66/11	26	4	12	16	3	AUB	+	LG	LG	INFLAM	CERVICITIS	
67	67/11	44	4	13	20	2	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 2
68	68/11	60	4	13	15	5	WHITE DIS	_	POST MENO	POST MENO	INFLAM	CERVICITIS	
69	69/11	62	4	14	19	3	AUB	+	POST MENO	POST MENO	CERVICITIS	ATROPH	CERVICITIS

70	70/11	40	4	13	16	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
71	71/11	49	4	14	25	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
72	72/11	30	5	13	17	2	WHITE DIS	+	_	_	NOR	CERVICITIS	
73	73/11	39	3	12	22	2	WHITE DIS	+	HG	HG	CERVICITIS	CERVICITIS	LG CIN
74	74/11	36	4	13	25	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
75	75/11	40	4	12	16	3	POST COITAL BLEED	+	INV CA	INV CA	ADENO CA	ADENO CA	PD ADENOCA
76	76/11	65	4	13	16	6	AUB	_	INV CA	INV CA	SCC	SCC	WD SCC
77	77/11	63	4	13	23	3	AUB	+	POST MENO	POST MENO	ATROPH	ATROPH	
78	78/11	42	4	14	17	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
79	79/11	45	5	13	21	3	WHITE DIS	+	_	_	CERVICITIS	INFLAM	CERVICITIS
80	80/11	38	4	14	21	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
81	81/11	24	5	13	17	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
82	82/11	29	4	12	17	2	WHITE DIS	+	_	_	INFLAM	OESTROG	
83	83/11	49	4	14	24	5	AUB	+	_	_	CERVICITIS	CERVICITIS	
84	84/11	33	4	12	22	2	PRURITIS	+	_	_	INFLAM	INFLAM	
85	85/11	40	5	12	20	2	WHITE DIS	+	_	_	PROGEST	CERVICITIS	
86	86/11	40	4	13	25	2	AUB	+	_	_	PROGEST	PROGEST	
87	87/11	29	5	12	18	3	AUB	+	_	_	INFLAM	CERVICITIS	
88	88/11	35	4	13	18	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
89	89/11	43	5	14	19	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
90	90/11	51	4	13	20	3	AUB	+	_	_	ATROPH	ATROPH	
91	91/11	30	5	12	16	2	WHITE DIS	+	_	_	OESTROG	OESTROG	

92	92/11	45	5	13	26	2	PRURITIS	+	_	_	OESTROG	CERVICITIS	
93	93/11	55	3	13	16	4	PAIN ABD	+	_	_	CERVICITIS	CERVICITIS	
94	94/11	30	3	14	20	3	PAIN ABD	+	_	_	INFLAM	OESTROG	CERVICITIS
95	95/11	35	4	14	23	3	WHITE DIS	+	_	_	INFLAM	INFLAM	
96	96/11	28	2	13	17	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
97	97/11	20	5	13	18	1	WHITE DIS	_	_	_	INFLAM	INFLAM	
98	98/11	42	5	14	20	2	PAIN ABD	+	_	_	INFLAM	INFLAM	
99	99/11	38	3	13	21	2	WHITE DIS	+	_	_	INFLAM	INFLAM	
100	100/11	36	4	14	18	0	WHITE DIS	_	_	_	CERVICITIS	CERVICITIS	
101	101/11	32	4	12	16	2	PAIN ABD	+	LG	LG	CERVICITIS	CERVICITIS	CIN 1
102	102/11	55	5	13	16	3	AUB	_	INV CA	INV CA	SCC	SCC	MD SCC
103	103/11	30	3	14	24	2	PAIN ABD	+	_	_	CERVICITIS	CERVICITIS	
104	104/11	40	3	12	15	2	WHITE DIS	+	_	_	OESTROG	OESTROG	
105	105/11	75	5	13	20	6	WHITE DIS	_	ECTOPY	ECTOPY	CERVICITIS	CERVICITIS	CERVICITIS
106	106/11	39	4	14	23	2	WHITE DIS	+	_	_	NOR	NOR	
107	107/11	38	4	13	15	6	WHITE DIS	+	SATELLITE LES	SATELLITE LES	CERVICITIS	LSIL	CERVICITIS
108	108/11	26	5	14	21	1	WHITE DIS	_	ECTOPY	ECTOPY	LSIL	LSIL	CIN 1
109	109/11	26	5	13	22	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
110	110/11	48	5	13	18	3	WHITE DIS	+	LG	LG	CERVICITIS	CERVICITIS	
111	111/11	45	4	13	23	3	PRURITIS	+	NOR	NOR	CERVICITIS	CERVICITIS	
112	112/11	23	4	12	18	1	AUB	_	_	_	CERVICITIS	CERVICITIS	
113	113/11	25	4	13	20	2	WHITE DIS	+	ECTOPY	ECTOPY	CERVICITIS	CERVICITIS	

114	114/11	40	2	14	17	2	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 2-3
115	115/11	55	4	13	17	3	AUB	+	LG	LG	ASCUS	CERVICITIS	CHRONIC CERVICITIS WITH FOCAL CIN 1 CHANGES
116	116/11	40	5	13	18	3	WHITE DIS	_	HG	HG	HSIL	HSIL	CIN 3
117	117/11	40	4	12	16	3	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 2-3
118	118/11	40	3	13	15	2	AUB	+	HG	HG	HSIL	HSIL	CIN 2
119	119/11	60	3	14	15	3	AUB	+	INV CA	INV CA	SCC	SCC	SCC-WD KERATINISING
120	120/11	55	5	13	17	2	AUB	+	INV CA	INV CA	SCC	SCC	SCC-MD LARGE CELL TYPE
121	121/11	35	5	13	18	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
122	122/11	32	5	14	19	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	CERVICITIS
123	123/11	34	3	13	19	2	PAIN ABD	+	HG	HG	HSIL	HSIL	CIN 2-3
124	124/11	29	5	13	20	2	WHITE DIS	+	LG	LG	LSIL	LSIL	CIN 2
125	125/11	45	4	15	17	5	PAIN ABD	_	LG	LG	CERVICITIS	CERVICITIS	
126	126/11	65	3	14	45	5	AUB	_	INV CA	INV CA	SCC	SCC	SCC-WD KERATINISING
127	127/11	35	5	14	25	4	WHITE DIS	+	ECTOPY	ECTOPY	LSIL	LSIL	CIN 1
128	128/11	49	5	12	29	1	AUB	+	INV CA	INV CA	SCC	SCC	SCC-WD KERATINISING
129	1/12	27	3	13	19	2	WHITE DIS	+	NOR	NOR	CERVICITIS	CERVICITIS	
130	2/12	50	5	13	15	4	POST COITAL BLEED	+	INV CA	INV CA	SCC	SCC	SCC-WD KERATINISING
131	3/12	45	3	14	17	3	WHITE DIS	+	_	_	CERVICITIS	INADEQ	
132	4/12	35	2	13	16	3	AUB	_	HG	HG	INADEQ	HSIL	CIN 2
133	5/12	40	4	13	18	3	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 2
134	6/12	30	4	15	20	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
135	7/12	31	5	13	20	3	WHITE DIS	+	LG	LG	INFLAM	LSIL	CIN 1

136	8/12	48	3	13	25	2	PAIN ABD	+	_	_	CERVICITIS	CERVICITIS	
137	9/12	58	3	13	18	2	AUB	_	INV CA	INV CA	SCC	SCC	CA IN SITU WITH FOCAL MICROINVASION
138	10/12	55	5	13	19	8	WHITE DIS	_	_	_	ATROPH	ATROPH	
139	11/12	42	5	14	20	2	WHITE DIS	+	HG	HG	INADEQ	HSIL	CIN 2
140	12/12	46	4	13	16	3	PAIN ABD	+	LG	LG	ASCUS	LSIL	CIN 1
141	13/12	48	5	13	18	4	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	CERVICITIS
142	14/12	51	5	14	17	5	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
143	15/12	37	3	13	17	1	PAIN ABD	+	_	_	CERVICITIS	CERVICITIS	
144	16/12	30	4	13	22	0	PRURITIS	_	_	_	CERVICITIS	CERVICITIS	
145	17/12	28	5	13	18	2	WHITE DIS	+	LG	LG	CERVICITIS	CERVICITIS	
146	18/12	34	5	12	23	3	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
147	19/12	52	5	13	16	1	AUB	+	_	_	ATROPH	ATROPH	
148	20/12	45	5	13	15	3	PAIN ABD	+	_	_	NEG FOR SIL	INADEQ	
149	21/12	54	3	14	22	5	AUB	+	INV CA	INV CA	SCC	SCC	PD SCC
150	22/12	45	2	13	17	2	POST COITAL BLEED	+	_	_	NEG FOR SIL	NEG FOR SIL	
151	23/12	45	5	14	20	3	WHITE DIS	+	_	_	NEG FOR SIL	NEG FOR SIL	
152	24/12	38	4	13	22	2	WHITE DIS	+	_	_	INADEQ	NEG FOR SIL	
153	25/12	49	5	13	19	1	WHITE DIS	_	_	_	CERVICITIS	CERVICITIS	
154	26/12	49	5	14	20	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
155	27/12	30	3	13	17	2	WHITE DIS	+	_	_	INFLAM	INFLAM	
156	28/12	59	2	14	19	3	PAIN ABD	+	_	_	INADEQ	ATROPH	
157	29/12	35	3	13	19	2	AUB	+	_	_	CERVICITIS	CERVICITIS	
158	30/12	44	3	13	19	2	PAIN ABD	+	ECTOPY	ECTOPY	INADEQ	CERVICITIS	
159	31/12	50	5	14	20	1	WHITE DIS	_	_	_	CERVICITIS	CERVICITIS	
160	32/12	50	5	13	20	3	WHITE DIS	+	LG	LG	LSIL	LSIL	CIN 1

161	33/12	45	5	13	25	2	PAIN ABD	+	SATELLITE LES	SATELLITE LES	CERVICITIS	CERVICITIS	
162	34/12	35	5	12	17	2	WHITE DIS	+	_	_	INFLAM	LSIL	CERVICITIS
163	35/12	25	4	13	17	2	WHITE DIS	+	LG	LG	CERVICITIS	NEG FOR SIL	
164	36/12	55	3	14	19	3	AUB	+	SATELLITE LES	SATELLITE LES	LSIL	LSIL	CIN 1
165	37/12	25	3	13	20	1	WHITE DIS	_	LG	LG	CERVICITIS	CERVICITIS	
166	38/12	50	5	14	16	2	WHITE DIS	+	POST MENO	POST MENO	INFLAM	CERVICITIS	
167	39/12	43	5	14	30	2	PAIN ABD	_	NOR	NOR	INFLAM	NEG FOR SIL	
168	40/12	45	3	12	16	5	PAIN ABD	_	_	_	CERVICITIS	CERVICITIS	
169	41/12	55	5	13	22	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
170	42/12	40	4	14	25	2	WHITE DIS	+	_	_	CERVICITIS	CERVICITIS	
171	43/12	46	5	13	20	2	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 2
172	44/12	41	3	13	21	2	PRURITIS	+	_	_	CERVICITIS	CERVICITIS	CERVICITIS
173	45/12	36	5	13	17	2	WHITE DIS	+	_	_	NOR	NOR	
174	46/12	28	3	14	21	0	WHITE DIS	_	NOR	NOR	PROGEST	PROGEST	
175	47/12	39	3	13	17	1	WHITE DIS	_	_	_	PROGEST	PROGEST	
176	48/12	42	5	13	20	1	WHITE DIS	_	NOR	NOR	CERVICITIS	CERVICITIS	
177	49/12	32	4	14	20	2	PAIN ABD	+	POLYP	POLYP	CERVICITIS	CERVICITIS	
178	50/12	50	4	14	38	2	WHITE DIS	+	NOR	NOR	CERVICITIS	CERVICITIS	
179	51/12	38	5	13	18	2	PAIN ABD	+	ECTOPY	ECTOPY	CERVICITIS	CERVICITIS	
180	52/12	29	5	13	19	2	WHITE DIS	+	SATELLITE LES	SATELLITE LES	INFLAM	CERVICITIS	
181	53/12	32	3	13	22	2	WHITE DIS	+	LG	LG	LSIL	LSIL	CIN 1
182	54/12	35	5	15	20	1	WHITE DIS	_	_	_	CERVICITIS	CERVICITIS	CERVICITIS
183	55/12	40	5	13	15	3	AUB	+	INV CA	INV CA	SCC	SCC	WD SCC-LARGE CELL TYPE
184	56/12	41	3	14	19	1	AUB	_	HG	HG	HSIL	HSIL	CIN 2

185	57/12	46	4	13	17	2	WHITE DIS	+	LG	LG	LSIL	LSIL	CHRONIC CERVICITIS WITH FOCAL CIN 1 CHANGES
186	58/12	32	5	13	17	2	WHITE DIS	+	LG	LG	LSIL	LSIL	CHRONIC CERVICITIS WITH FOCAL CIN 1 CHANGES
187	59/12	38	3	13	16	2	PAIN ABD	+	LG	LG	CERVICITIS	CERVICITIS	CERVICITIS
188	60/12	36	5	14	20	2	WHITE DIS	+	LG	LG	LSIL	LSIL	CIN 1
189	61/12	42	5	13	18	3	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 2
190	62/12	50	5	13	19	3	AUB	+	HG	HG	HSIL	HSIL	CIN 2-3
191	63/12	45	4	14	20	2	WHITE DIS	+	LG	LG	LSIL	LSIL	CIN 1
192	64/12	32	3	13	24	2	PAIN ABD	+	NOR	NOR	CERVICITIS	CERVICITIS	
193	65/12	40	3	13	18	4	WHITE DIS	+	LG	LG	INFLAM	CERVICITIS	CERVICITIS
194	66/12	39	4	14	19	1	PAIN ABD	_	HG	HG	INADEQ	HSIL	CIN 2-3
195	67/12	55	4	13	20	3	AUB	+	INV CA	INV CA	SCC	SCC	PD SCC
196	68/12	36	5	14	18	3	POST COITAL BLEED	+	INV CA	INV CA	SCC	SCC	MD SCC
197	69/12	65	5	15	19	5	AUB	_	INV CA	INV CA	SCC	SCC	PD SCC
198	70/12	28	3	14	18	3	WHITE DIS	+	HG	HG	HSIL	HSIL	CIN 1
199	71/12	60	4	14	16	5	PAIN ABD	_	INV CA	INV CA	SCC	SCC	PD SCC
200	72/12	46	2	13	22	2	WHITE DIS	+	LG	LG	INFLAM	CERVICITIS	CERVICITIS

KEY TO MASTER CHART

SE STATUS	: Socioeconomic status
PS	: Puerperal sterilisation
CONV PAP	: Conventional Pap smear
WHITE DIS	: White discharge per vagina
AUB	: Abnormal uterine bleeding
PAIN ABD	: Pain abdomen
LG	: Low grade lesion
HG	: High grade lesion
INV CA	: Invasive carcinoma
POST MENO	: Postmenopausal changes
NOR	: Normal
SATELLITE LES	: Satellite lesion
INADEQ	: Inadequate smear
ATROPH	: Atrophic smear
INFLAM	: Inflammatory smear
NEG FOR SIL	: Negative for Squamous Intraepithelial Lesion
OESTROG	: Oestrogenic phase
PROGES	: Progestrogenic phase
ADENOCA	: Adenocarcinoma
CA IN SITU	: Carcinoma in situ
LG CIN	: Low grade Cervical Intraepithelial Neoplasia
MD ADENOCA	: Moderately differentiated Adenocarcinoma
PD ADENOCA	: Poorly differentiated Adenocarcinoma
WD SCC	: Well differentiated Squamous Cell Carcinoma
MD SCC	: Moderately differentiated Squamous Cell Carcinoma
PD SCC	: Poorly differentiated Squamous Cell Carcinoma

ABSTRACT

INTRODUCTION:

Carcinoma cervix is one of the leading causes of death among women in developing countries. For each case of cancer of body of the uterus, there are 25 cases of cancer cervix in India. About 5,00,000 new cases of carcinoma cervix are being diagnosed each year out of which 79% occur in the developing countries.

AIM:

By virtue of its accessibility, cancer of cervix can be readily diagnosed in its precancerous stage. If treated in the earlier stages the patient can often be cured of the disease. There are various methods of screening for carcinoma cervix.

The aim of this study is to compare the efficacy of VIA, VILI, conventional Pap smear and LiquiPrep™ as screening procedure for carcinoma cervix in patients attending the Gynecology department of Institute of social obstetrics and Govt. Kasturba Gandhi hospital,Chennai and to correlate the cytological findings with histopathological diagnosis.

MATERIALS AND METHODS:

VIA, VILI, conventional pap smear cytology and liquid based cytology was done in all cases. Both conventional and liquid based cytology smears were

stained by routine Pap stain. Those cases showing VIA/VILI Positive (or) cytology positive were subjected to cervical biopsy. For few VIA/VILI Negative cases, biopsy was done (as control).

RESULTS:

Both VIA/VILI and LBC had similar sensitivity rates in the screening of cancer cervix compared to conventional pap smear. However the specificity and PPV were highest for the conventional pap smear followed by Liquiprep™. Liquiprep™ had the highest negative predictive value.

CONCLUSION:

In conclusion, VIA/VILI can be used as an initial screening test for cervical cancer in a low resource country like India. The false negative and false positive cases in this study can be minimized by proper screening and interpretation and further follow up by cytological smears. Conventional pap because of its high specificity can be used for followup of low grade lesions on colposcopy. LiquiPrep™ has a higher sensitivity equal to that of VIA/VILI and a comparatively higher specificity compared to VIA/VILI and therefore can be used for screening in conditions where there are no financial constraints.

KEYWORDS:

Carcinoma cervix, VIA, VILI, conventional pap smear, LiquiPrep™.